The Early Feasibility Study of the TMVR Transseptal System
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Medtronic **Clinical Investigation Plan**	
Clinical Investigation Plan/ Study Title	Evaluation of the Safety and Performance of The Medtronic Intrepid™ Transcatheter Mitral Valve Replacement System with Transfemoral Transseptal access in Patients with Moderate-Severe or Severe, Symptomatic Mitral Regurgitation – The Early Feasibility Study of the TMVR Transseptal System
Clinical Investigation Plan Identifier	MDT19042TMV002
Study Product Name	The Intrepid™ Transcatheter Mitral Valve Replacement (TMVR) System – designed for transfemoral access enabling transseptal delivery of a self-expanding bioprosthetic valve within the mitral valve
Sponsor/Local Sponsor	Medtronic, Inc. 8200 Coral Sea St NE Mounds View, MN 55112 United States
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Table of Contents

1. Glossary

Term	Definition
ADE	Adverse Device Effect
AE	Adverse Event
AKI	Acute Kidney Injury
ASD	Atrial Septal Defect
BNP	B-type Natriuretic Peptide
BSE	Bovine Spongiform Encephalopathy
ASADE	Anticipated Serious Adverse Device Effect
CA	Competent Authority
CEC	Clinical Event Committee
CFR	Code of Federal Regulation
CIP	Clinical Investigation Plan
CK/CK-MB	Creatine Kinase / Creatine Kinase Myocardial B fraction
COPD	Chronic Obstructive Pulmonary Disease
CRO	Clinical Research Organization
CRT-D	Cardiac Resynchronization Therapy Device
CRF	Case Report Form
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
CVA	Cerebrovascular Accident
DAPT	Dual Antiplatelet Therapy
DD	Device Deficiency

Term	Definition
DES	Drug Eluting Stent
DMC / DSMB	Data Monitoring Committee / Data Safety Monitoring Board
DoH	Declaration of Helsinki
DTL	Delegated Task List
DVT	Deep Vein Thrombosis
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
EFS	Early Feasibility Study
EROA	Effective Regurgitant Orifice Area
FAL	Foreseeable Adverse Event List
FD	Financial Disclosure
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FEV1	Forced Expiratory Volume
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GI	Gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator Brochure
IC/ICF	Informed Consent/Informed Consent Form
ICD	Implantable Cardiac Defibrillator
ICH	International Conference of Harmonization

Term	Definition
ICU	Intensive Care Unit
IDE	Investigational Device Exemption
IFU	Instructions For Use
ICU	Intensive Care Unit
INR	International Normalized Ratio
IPG	Implantable Pulse Generator
IRB	Institutional Review Board
IVC	Inferior Vena Cava
KCCQ	Kansas City Cardiomyopathy Questionnaire
LV	Left Ventricle
LVAD	Left Ventricular Assist Device
LVEDD	Left Ventricular End Diastolic Diameter
LVEDV	Left Ventricular End Diastolic Volume
LVEF	Left Ventricular Ejection Fraction
LVOT	Left Ventricular Outflow Tract
MDCT	Multi-Dimensional Computed Tomography
MDD	Medical Device Directive
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour, and Welfare
MI	Myocardial Infarction
MR	Mitral Regurgitation
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Score

Term	Definition
MVARC	Mitral Valve Academic Research Consortium
NSR	Non-Significant Risk
NYHA	New York Heart Association
PA	Pulmonary Artery
PCI	Percutaneous Coronary Intervention
PHI	Protected Health Information
PI	Principal Investigator
PPI	Permanent Pacemaker Implant
PVL	Paravalvular Leak
QoL	Quality of Life
RA	Regulatory Authority
RED	Radio Equipment Directive
RPI	Report of Prior Investigations
RSVP	Right Systolic Ventricular Pressure
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SF-12	Short Form (12) Health Survey
SAP	Statistical Analysis Plan
SC	Steering Committee
SR	Significant Risk
SID	Subject Identification
STS	Society of Thoracic Surgeons
STS-PROM	Society of Thoracic Surgeons Predictive Risk of Mortality

Term	Definition
TAVI	Transcatheter Aortic Valve Implantation
TEE	Transesophageal Echocardiogram
TIA	Transient Ischemic Attack
TMVR	Transcatheter Mitral Valve Replacement
TTE	Transthoracic Echocardiogram
TVL	Transvalvular Leak
UAE	Unavoidable Adverse Event
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
WBC	White Blood Count
6MWT	Six Minute Walk Test

2. Synopsis

Title	Evaluation of the Safety and Performance of The Medtronic Intrepid™ Transcatheter Mitral Valve Replacement System with Transfemoral Transseptal access in Patients with Moderate-Severe or Severe, Symptomatic Mitral Regurgitation – The Early Feasibility Study of the Intrepid™ TMVR Transseptal System
Clinical Study Type	Early Feasibility Study
Product Name	The Intrepid™ Transcatheter Mitral Valve Replacement (TMVR) System
Sponsor / Funding Source	Medtronic, Inc. 8200 Coral Sea St NE Mounds View, MN 55112 United States
External Organizations	Clinical Events Committee (CEC) / Data Monitoring Committee (DMC): BAIM Institute for Clinical Research 930 Commonwealth Ave, 3rd Floor

	Boston, MA 02215 Echocardiography Core Laboratory: Mayo Clinic Core Laboratory 200 First Street SW Rochester, MN 55905 Medidata Solutions, Inc. (imaging sharing network): Medidata Solutions, Inc. 350 Hudson Street, 9th Floor New York, NY 10014
Indication under investigation	Medtronic Intrepid™ TMVR System is intended for use as a replacement mitral valve for treatment of moderate-severe or severe symptomatic mitral regurgitation who by agreement of the local site multidisciplinary heart team experienced in mitral valve therapies may not be optimally treated with approved transcatheter repair or surgical mitral valve intervention.
Investigation Purpose	The purpose of this early feasibility study is to evaluate the safety and performance of The Intrepid™ TMVR System with transseptal access in patients with moderate-severe or severe, symptomatic mitral regurgitation, who are ineligible for conventional mitral valve surgery.
Product Status	Investigational
Primary Objective	The primary objective is to evaluate the safety of The Intrepid™ TMVR System by assessment of the nature, severity and frequency of complications associated with the delivery and/or implantation of the device.
Secondary Objectives	The secondary objective is to evaluate the performance of The Intrepid™ TMVR System 1. The degree of improvement of MR grade and symptoms, and the durability of TMVR function 2. The ability to accurately deliver and place the implant within the anatomy 3. The fit of the implant within the anatomy, including fixation, sealing and compatibility with structures (e.g., other components of the mitral valve apparatus, the conduction system, and the left ventricular outflow tract/aortic valve)
Study Design	Multi-center, prospective, non-randomized, investigational, early feasibility study in patients with moderate-severe or severe, symptomatic mitral regurgitation, who are ineligible for conventional mitral valve surgery with a follow up period of 5 years post-index procedure.

Sample Size	Since this is a limited clinical investigation, this study will enroll and treat up to 45 subjects at up to 15 investigational sites in the United States who require replacement of their mitral valve because of moderate-severe or severe, symptomatic mitral regurgitation, but are ineligible for conventional mitral valve surgery
Inclusion Criteria	**The subject must meet ALL of the following criteria:** 1. Heart Team agrees that a patient is a candidate for bioprosthetic mitral valve replacement 2. Subjects with moderate-severe or severe symptomatic mitral regurgitation who are determined by a multidisciplinary heart team to be a candidate for bioprosthetic mitral valve replacement and are ineligible for conventional mitral valve surgery based on predicted risk of operative mortality or irreversible major morbidity ≥ 35% and <50% at 30 days 3. Subject anatomically suitable for the Intrepid TMVR delivery system including transfemoral and transseptal access 4. Subject and the treating physician agree that the subject will return for all required post-procedure follow-up visits 5. Subject meets the legal minimum age to provide informed consent based on local regulatory requirements
Exclusion Criteria	**The subject may not meet any of the following criteria:** 1. Estimated life expectancy of less than 12 months due to associated non-cardiac co-morbid conditions 2. Prior transcatheter mitral valve procedure with device currently implanted 3. Prior transseptal intervention with occlusion device currently implanted 4. Anatomic contraindications for Intrepid™ TMVR (e.g., annular dimensions, high risk of LVOT obstruction, etc.) 5. Anatomically prohibitive mitral annular calcification (MAC) 6. Aortic valve disease requiring intervention or previous intervention within 90 days of enrollment 7. Severe tricuspid regurgitation 8. Patients unsuitable for implantation because of congenital abnormalities of the IVC, thrombosis of the femoral vein and/or of IVC, history of venous stents (iliac and/or femoral), presence of a vena cava filter or intracardiac mass or intracardiac thrombus 9. Right-sided congestive heart failure with echocardiographic evidence of severe right ventricular dysfunction 10. Pulmonary hypertension with resting pulmonary artery systolic pressures ≥ 2/3 systemic pressure

	11. Left ventricular ejection fraction (LVEF) <30% 12. Left ventricular end diastolic diameter (LVEDD) > 75mm 13. Hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, or other structural heart disease causing heart failure other than dilated ischemic or non-ischemic cardiomyopathy 14. Infiltrative cardiomyopathies (e.g., amyloidosis, hemochromatosis, sarcoidosis) 15. Subject is contraindicated for transesophageal echocardiography (TEE) 16. Need for emergent or urgent cardiac or non-cardiac surgery 17. Hemodynamic instability requiring dependency of either inotropic agents or mechanical circulatory support 18. Subject refuses a blood transfusion 19. Subject unwilling or unable to adhere to the protocol specified anticoagulation treatment 20. Blood dyscrasias as defined: leukopenia (WBC <1000 cells/mm^3), thrombocytopenia (platelet count <50,000 cells/mm^3) 21. History of bleeding diathesis or coagulopathy that precludes anticoagulation 22. Active gastrointestinal (GI) bleeding that would preclude anticoagulation 23. Known hypersensitivity or contraindication to nitinol, , or sensitivity to contrast media which cannot be adequately pre-medicated 24. Any cardiac or peripheral interventional procedure performed within 30 days prior to enrollment in patients treated with bare-metal stent or drug-eluting stent (DES) with approved 1-month DAPT labeling or within 90 days prior to enrollment for subjects treated with DES without approved 1-month labeling. 25. Untreated clinically significant coronary artery disease requiring revascularization 26. Severe symptomatic carotid stenosis 27. Stroke or TIA within 90 days of enrollment 28. Evidence of an acute myocardial infarction within 90 days prior to enrollment 29. Active endocarditis or active infection requiring antibiotic therapy

	30. Implant of any Cardiac Resynchronization Therapy (CRT) or Cardiac Resynchronization Therapy with cardioverter-defibrillator (CRT-D) within 90 days of enrollment 31. End stage renal disease requiring chronic dialysis or creatinine clearance < 30 cc/min within 30 days of the Index Procedure 32. Severe Chronic Obstructive Pulmonary Disease (COPD) demonstrated by Forced Expiratory Volume (FEV1) < 750cc 33. Pregnancy, breastfeeding, or intent to become pregnant prior to completion of all protocol follow-up requirements 34. Currently participating in an investigational drug or another device study that has not yet reached its primary endpoint 35. Other medical, social, or psychological conditions that in the opinion of the Investigator precludes the subject from appropriate consent or adherence to the protocol required follow-up exams
Study Procedures and Assessments	[See Table 2: Schedule of Events Table]
Safety Assessments	Serious adverse events, device deficiencies, and non-serious adverse events will be collected from the time of enrollment until the end of the study or until study exit, whichever comes first. The safety assessment performed during this study will be based on the relatedness to the TMVR implant and index procedure.
Statistics	Study results will be summarized using standard descriptive statistics. The sample size is based upon industry standards for early feasibility stage studies of medical devices; the sample size is not statistically derived, as this is not a hypothesis-testing study.

3. Introduction

3.1 Background

Mitral regurgitation (MR) is a common form of valve disease and affects up to 10% of the general population. Mitral valve replacement surgery is an established form of treatment for MR, however less than 50% of patients are referred to surgery (1). The overall 5-year mortality rate for unoperated patients has been reported to be up to 50% and the proportion of surviving patients hospitalized for heart failure increased from 41% in the first year to 90% by 5 years(2). This lack of surgical referral signifies the need for alternative MR treatments and is in part due to a large subset of patients classified as poor surgical candidates. There is also a cohort of patients suffering from secondary MR and future treatment options for this population remain unclear(3,4).

Percutaneous mitral valve repair has been commercially available in the United States since 2013 and in Europe since 2008 as an option for less invasive approach for treatment of MR. While acute procedural

success has been reported to be greater than 90%, repair has also been associated with a higher rate of reoccurrence of MR compared to replacement. This increased durability with replacement could have important long-term outcomes(5,6).

The investigational device is not approved in any geography and is called the Intrepid™ Transcatheter Mitral Valve Replacement (TMVR) System, manufactured by Medtronic. The Intrepid™ TMVR implant is intended to function similarly to a standard bioprosthetic valve implant, in that it allows blood to flow only in the forward direction, thereby preventing mitral regurgitation. A standard valve implant, however, is sewn directly into the heart during surgery in which the chest is fully open, the patient is put on cardiopulmonary bypass support and the heart is temporarily stopped. The Intrepid™ TMVR implant is intended to be placed through a less invasive procedure, not requiring thoracotomy, cardiopulmonary bypass support and cardioplegia, thereby potentially reducing the surgical risks. Based on the current clinical experience, the Intrepid TMVR system is performing as intended with successful implant procedures and proper function of the TMVR valve.

The Intrepid™ TMVR system has previously been designed and investigated using transapical access for delivery of a self-expanding bioprosthetic valve within the mitral valve. Transapical access was the common initial approach during the first decade of transcatheter aortic valve replacement but has since declined due to evidence of worse clinical outcomes compared to transfemoral approach. Transapical complications include but are not limited to impairment of the left ventricular function, excessive bleeding, development of atrial fibrillation, and pleural effusion (7). New transcatheter transseptal interventions for patients with MR has been gaining interest and multiple systems are in early phase of development particularly with mitral valve replacement (8). Data from MitraClip valve repair system has also confirmed procedural success of transseptal access for treatment of MR (6).

3.2 Purpose

The purpose of this early feasibility study is to evaluate the safety and performance of The Intrepid™ TMVR System with transseptal access in patients with moderate-severe or severe, symptomatic mitral regurgitation, who are ineligible for conventional mitral valve surgery.

4. Objectives and Endpoints

4.1 Objectives

4.1.1 Primary Objective

The primary objective of the study is to evaluate the safety of the Intrepid™ TMVR System by assessing the nature, severity and frequency of complications associated with the delivery and/or implantation of the device.

4.1.2 Secondary Objective

The secondary objective of the study is to evaluate the performance of the Intrepid™ TMVR System by assessing the following:

- The degree of improvement of MR grade and symptoms, and the durability of TMVR function
- The ability to accurately deliver and place the implant within the anatomy
- The fit of the implant within the anatomy, including fixation, sealing and compatibility with structures (e.g., other components of the mitral valve apparatus, the conduction system and the left ventricular outflow tract/aortic valve)

4.2 Study Endpoints

4.2.1 Primary Safety Endpoint

The primary safety endpoint is implant, delivery or device related serious adverse events (through 30 days post-procedure).

4.2.2 Secondary Performance Endpoints

- Successful access, delivery of implant, and retrieval of the delivery system
- Reduction in MR Grade from baseline (measured by echo through 30 days post-procedure)
- No significant MV stenosis (measured by echo through 30 days post-procedure)
- LV outflow tract (LVOT) patency (measured by echo through 30 days post-procedure)
- Change in NYHA Class from baseline (through 30 days post-procedure)

4.2.3 Additional exploratory endpoints:

- Measured by echo post-procedure through 5 years:
  - Reduction in MR Grade from baseline
  - No significant MV stenosis
  - LV outflow tract (LVOT) patency
  - Improvement in LVEF
  - Improvement in cardiac output/cardiac index
  - Reduction in LV end-systolic and end-diastolic dimensions
  - Presence of intra-atrial shunt with clinically significant pressure gradient requiring closure device
- Change in NYHA Class from baseline
- Change in 6MWT from baseline
- Change in QoL from baseline
- Procedural times (e.g., deployment time, access duration, rapid pacing duration)
- Re-hospitalizations for heart failure
- MVARC defined outcomes of: (see Appendix 17.1 for specific definitions)
  - Technical success upon exit from operating room
  - Device success at 30 days and 1 year

- Procedural success at 30 days
- Individual subject success at 1 year

5. Study Design

The Early Feasibility Study of the Intrepid™ TMVR Transseptal System is designed as a multi-center, prospective, non-randomized, investigational, early feasibility study to evaluate the safety and performance of transcatheter mitral valve replacement in patients with moderate-severe or severe, symptomatic mitral regurgitation who are deemed ineligible for conventional mitral valve surgery by the heart team. Subjects will be followed 5 years post-implant. The study methods include the following measures to minimize potential sources of bias:

- An external, independent Clinical Events Committee (CEC) will review and adjudicate, at minimum, all deaths and endpoint related adverse events. Safety endpoint results will be based on CEC adjudications.
- All sites will follow a standardized protocol for acquisition of echocardiographic endpoint data.
- Core labs will evaluate all echocardiograms. Echocardiographic trial endpoint results will be based on Core Lab assessments.
- Subjects will be screened to confirm eligibility for enrollment with pre-defined inclusion and exclusion criteria.

5.1 Duration

The enrollment period is estimated to be approximately two (2) years and subjects will be followed for up to five years post index procedure; therefore, the estimated total duration of the study (first subject enrolled to last subject completing his/her last follow-up exam) is estimated to be 7 years.

5.2 Rationale

Study design is based on industry standards and risk assessment for early feasibility stage studies of medical devices. The basis for the selection of the study endpoints include:

- Clinically relevant outcomes for mitral valve replacement devices, that are
- Objectively defined and measurable in the majority of subjects

5.3 Study Oversight

The study will utilize an Executive Committee. This committee will advise on the scientific content of the study and provide input for the execution. Members may include study site investigators. The purpose of this committee is to provide unbiased opinions and expertise to the clinical study design and process. The committee will support the execution of the trial and provide guidance, feedback and direction to the study. Additional details, including committee membership, can be found in the Study Governance Committee Charter.

A Screening Committee will be utilized to ensure subject selection is appropriate and consistent across study sites. The Screening Committee will include a minimum of: an interventional cardiologist, a cardiothoracic surgeon, an echocardiologist and a heart failure specialist. Prior to the onset of the study, the Screening Committee will establish a charter that describes its roles, responsibilities, and processes. Final decisions on subject eligibility will be made by the Screening Committee.

6. Product Description

6.1 General

The Intrepid™ Transcatheter Mitral Valve Replacement (TMVR) System consists of the following components: an implantable bioprosthesis, a delivery system, and a loading system.

The Intrepid™ TMVR bioprosthesis is comprised of three structures. The inner Nitinol stent supports a bioprosthetic valve composed of bovine pericardial tissue leaflets and woven polyester fabric. The outer Nitinol fixation ring structure engages the mitral valve annulus to provide fixation and sealing. As the inner stent and outer fixation ring structures are connected only at points along the ventricular rim, the fixation ring can conform to fit the dynamic anatomy of the mitral valve throughout the cardiac cycle, without distorting the inner stent or replacement valve. This isolation reduces the dynamic, asymmetrical loading of the valve leaflets and is intended to prolong valve durability and ensure consistent hemodynamics. In addition, a woven polyester skirt is attached to the top of the fixation ring and flares outward to form an atrial brim. The brim is reinforced with flexible Nitinol wire that is structurally independent of the fixation ring to allow each component to conform to the anatomy.

The delivery system is designed for transfemoral access and consists of a transfemoral dilator kit, transfemoral sheath with a transfemoral dilator, flow reverser, cradle, and a delivery catheter.

The bioprosthesis is compressed using Intrepid™ TMVR loading system before loading into the capsule. The delivery catheter is then used to deliver the bioprosthetic through the transfemoral sheath into the left atrium through the interatrial septum. When properly positioned (using fluoroscopy and echocardiography guidance), the capsule is retracted, to gradually deploy and fully release the self-expanding implant within the mitral valve.

Refer to Appendix ~~17.3~~17.3 Instructions for Use for additional details regarding the device description, packaging, sterilization and storage conditions

6.2 Manufacturer

Manufacturer details are provided in the Instructions for Use in Appendix 17.3 Instructions for Use.

6.3 Packaging

Labeling of the Intrepid™ TMVR System will be provided in English and the local language as required. The Medtronic Intrepid™ System is considered investigational and will carry the applicable labeling

required to indicate "For Investigational Use Only" as required by local regulations. The Intrepid™ TMVR System components are supplied sterile with some accessories provided non-sterile, and each packaged separately.

6.4 Intended Population

The Medtronic Intrepid™ TMVR System is intended for use in patients who have moderate-severe or severe symptomatic mitral regurgitation who are determined by a multidisciplinary heart team to be a candidate for bioprosthetic mitral valve replacement who are ineligible for conventional mitral valve surgery.

6.5 Equipment

Medtronic will provide the Merit Medical BasixTouch™ inflation device to sites. No other trial-specific equipment will be provided. Equipment used for assessing study variables (e.g., echocardiographic systems) should be maintained per the site's standard procedures. Maintenance and calibration reports may be monitored periodically by the monitor.

3mensio Workstation will be used by Medtronic for pre-operative planning and sizing for the TMVR procedure.

6.6 Product Use

Instructions for Use for the Medtronic Intrepid™ TMVR System is provided in Appendix 17.3– Instructions for Use.

6.7 Product Training Materials

Prior to a given site's first use of any investigational product site personnel directly involved in the Index Procedure will receive device training (if necessary, usage and handling of device under investigation). Training may be conducted via Site Initiation Visits, Investigator and Coordinator Meetings, Medtronic training facilities, and/or other media sessions. The sponsor will maintain documentation of attendance at each of these training opportunities, as applicable.

Additionally, Medtronic representative(s) will be present at each site's TMVR procedures as part of the ongoing training process.

6.8 Product Receipt and Tracking

Good Clinical Practice guidelines require accounting for the disposition of all investigational devices received by each clinical site. The Investigator is responsible for accounting for all used and unused devices. Sites are required to maintain investigational device records that contain the following information:

- Investigational device name
- Device Serial Numbers, if applicable
- Device Lot Numbers

- Expiration dates, if applicable
- Date of Receipt
- Name of person receiving the device
- Date of the implant or use
- ID number of the subject receiving or using the device
- Disposition (implanted, opened not used, disposed of, or returned to Medtronic)

6.9 Product Storage

The Intrepid™ TMVR System will be hand carried or shipped to the sites at intervals dependent on the rate of subject accrual. The site will use a device accountability form to document the inventory and study device disposition. All Intrepid™ TMVR devices must be stored at room temperature in an area free of environmental extremes and with limited access. Medtronic will inspect the storage area and will monitor device accountability. In addition, all information for the use, storage and handling of the investigational device as indicated in the Instructions for Use, must be taken into account.

Instructions for Use and storage recommendations are outlined in Appendix 17.3– Instructions for Use.

6.10 Product Return

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

- Device Serial Numbers, if applicable
- Device Lot Numbers
- Quantity and reason for the device being returned to Medtronic, or disposed of
- Name of the person who returned or disposed of each device
- Date of shipment back to Medtronic, or date of disposal

Following the completion of each index procedure, the investigator must return to Medtronic 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 Medtronic as well as all product usage including opened but non-implanted devices. All explanted devices should be returned to Medtronic for analysis when permissible by local laws and regulations. To receive a Returned Product Mailer Kit, please contact your local Medtronic field personnel.

6.11 Product Accountability

Access to investigational devices shall be controlled and the investigational devices shall be used only in the clinical investigation according to this CIP. Medtronic shall keep records to document the location of all investigational devices from shipment to sites until implant, return, or disposal. The Investigator or an authorized designee shall maintain a device accountability log documenting the receipt, use, return and disposal of all investigational devices at their site. When study enrollment is complete, the Investigator shall return any unused devices to Medtronic.

7. Study Site Requirements

7.1 Investigator/Investigation Site Selection

This trial may be conducted at up to 15 US sites with appropriate regulatory approval. Investigational sites will meet the following criteria:

- Presence or capacity of establishing an investigative team consisting of the following:
  - Interventional cardiologist
  - Cardiothoracic surgeon
  - Echocardiologist/Cardiac anesthesiologist
  - Heart failure specialist
  - Study coordinator(s)
- Presence or capacity of establishing multidisciplinary heart team consisting of the requirements outlined in Section 7.3.
- Investigators are not debarred, disqualified, or working under sanctions in applicable regions
- Access to an adequate number of eligible patients
- Adequate staff that is accessible and has time to manage the study for 7 days per week, 24 hours per day
- Willing to comply with the Clinical Investigation Plan and data requirements, including reporting Adverse Events
- Willing to comply with the Investigational Review Board (IRB)/ Ethics Committee (EC) and local regulatory requirements
- Non-invasive imaging including echocardiography, vascular ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI)
- Operating room or hybrid operating room/catheterization lab equipped with a fixed radiographic imaging system with flat-panel fluoroscopy, offering quality imaging
- All site personnel must provide his/her Curriculum Vitae. Additionally, each Investigator must sign and comply with the protocol-specific Investigator Agreement.
- Information on the investigational sites (i.e., name, address, PI, etc.) will be maintained in a separate document.

7.2 Site Principal Investigators

Each site will have two Co-Principal Investigators (PI), one who is an interventional cardiologist, and one who is a cardio(thoracic) surgeon. The Co-PIs have overall responsibility for the conduct of the study at the site, including protecting the rights, safety, and welfare of the study subjects at their site, the integrity of the study data generated by their site, and for ensuring the study is conducted in compliance with the Clinical Investigation Plan, 21 CFR 50, 11, 54, 56 and 812, the latest version of ISO 14155, the Declaration of Helsinki, International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, IRB/EC requirements and local regulations.

The site Co-PIs may also serve as members of the local Heart Team and/or Implant Team, as applicable.

7.3 Heart Team

Each site will utilize a local Heart Team, experienced in mitral valve therapies, to assess eligibility of each potential subject for the study.

At a minimum, the local Heart Team must include the following members:

- Interventional cardiologist
- Cardiothoracic surgeon
- Echocardiologist/Cardiac anesthesiologist
- Heart failure specialist

Individuals may only fulfill one role on the Heart Team. The site Co-PIs may also serve as members of the local Heart Team and/or Implant Team, as applicable.

7.4 Implant Team

Sites should establish a single implant team for all procedures and each Implant Team member must meet the minimum qualifications as outlined in Table 1 Implant team composition and roles will be defined for each site prior to activation and maintained for all investigational procedures.
The site Co-PIs may also serve as members of the local Heart Team and/or Implant Team, as applicable.

Table 1: Implant Team Membership [Minimum Qualifications]

Implant Team Member – Minimum Qualifications	
Cardiothoracic Surgeon: **Performing TMVR Procedures**	**Interventional Cardiologist:** **Performing TMVR Procedures**
• At least 5 years of experience post-residency – Cardiac surgery experience including contemporaneous transfemoral experience	• Interventional volume: – ≥250 catheterizations in the prior year – ≥25 structural heart procedures guided by TEE (eg, transcatheter mitral valve repair or replacement) in the prior year • ≥20 Transcatheter valve procedures in the prior year or ≥40 transcatheter valve procedures in the prior two years
Echocardiologist/Cardiac Anesthesiologist: **TEE Management during TMVR Procedures**	
• ≥25 structural heart procedures guided by TEE (e.g., transcatheter mitral valve repair or replacement) in the prior year	

7.5 Trial Training

Prior to investigational site involvement in trial activities, Medtronic (or designee) will provide study training relevant and pertinent to the involvement of personnel conducting trial activities, including investigator responsibilities, adverse event reporting as well as device training (if necessary, usage and

handling of device under investigation). Training requirements are outlined in the study-specific Training Plan. Training may be conducted via Site Initiation Visits, Investigator and Coordinator Meetings, and/or other multi-media sessions. Medtronic will maintain documentation of attendance at each of these training opportunities, as applicable.

Additionally, Medtronic representative(s) will be present at each site's TMVR procedures as part of the ongoing training process and provide technical support relative to the use of the investigational device.

7.6 Study Site Activation

All local and regional regulation requirements will be fulfilled prior to site activation and consenting of patients into the study. Medtronic and each investigational site must have written in documentation of site readiness, including, but not limited to:

- IRB approval letter (and voting list, as required by local law) of the current version of the CIP and Informed Consent Form (ICF.).
- Fully executed Clinical Trial Agreement (CTA)
- Financial Disclosure for Investigators
- Investigator Agreements
- Delegated Task List
- Training documentation

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

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

7.7 Role of the Sponsor Representatives

Sponsor representatives may provide support at the study site as required for the study under supervision of the Principal Investigator, including:

- Provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities
- Technical support at Index Procedure visit under the supervision of a study investigator, but no data entry, shall be performed by Medtronic personnel or their representatives at study sites

8. Selection of Subjects

8.1 Study Population

Since this is a limited clinical investigation, the study will enroll and treat up to 45 subjects (as approved by the FDA in 15 subject increments) at up to 15 investigational sites who require replacement of their

mitral valve because of moderate-severe or severe, symptomatic mitral regurgitation, but are ineligible for conventional mitral valve surgery.

Patients will be screened prior to study entry to determine if they meet the Eligibility Criteria. Patients who have signed an Informed Consent and fulfill the inclusion criteria and none of the exclusion criteria are eligible for enrollment.

8.2 Subject Enrollment

Subjects will be considered enrolled into the trial once the subject is documented as enrolled in the Oracle Electronic Data Capture (EDC) database system. Prior to enrollment the patient must sign informed consent. Enrollment will only occur after confirmation the patient meets all inclusion criteria, does not meet any exclusion criteria, has been assessed by the Heart Team as being an appropriate candidate for enrollment and approved by the Screening Committee.

Due to the inclusion/exclusion criteria, not all patients 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 who do not meet trial criteria, the reason for not continuing in the trial must be documented and recorded in the EDC system. Patients consented but not enrolled will be considered screen failures and no further trial-related follow-up will be required.

The study will enroll and treat up to 45 subjects (as approved by the FDA in 15 subject increments).

8.3 Inclusion Criteria

The subject must meet ALL of the following inclusion criteria:

1. Heart Team agrees that patient is a candidate for bioprosthetic mitral valve replacement
2. Subjects with moderate-severe or severe symptomatic mitral regurgitation who are determined by a multidisciplinary heart team to be a candidate for bioprosthetic mitral valve replacement and are ineligible for conventional mitral valve surgery based on predicted risk of operative mortality or irreversible major morbidity ≥ 35% and <50% at 30 days1
3. Subject anatomically suitable for the Intrepid TMVR delivery system including transfemoral and transseptal access
4. Subject and the treating physician agree that the subject will return for all required post-procedure follow-up visits
5. Subject meets the legal minimum age to provide informed consent based on local regulatory requirements

[1] The Early Feasibility Study of the TMVR Transseptal System utilizes a Heart Team approach to assess operative risk. The risk stratification is based on the STS predicted risk of operative mortality or irreversible major morbidity **in conjunction with** the Heart Team evaluation of additional risk factors including co-morbidities, frailty, heart failure status, and other factors not accounted for the in the risk calculation

8.4 Exclusion Criteria

The subject may not meet any of the following exclusion criteria:

1. Estimated life expectancy of less than 12 months due to associated non-cardiac co-morbid conditions
2. Prior transcatheter mitral valve procedure with device currently implanted
3. Prior transseptal intervention with occlusion device currently implanted
4. Anatomic contraindications for Intrepid™ TMVR (eg, annular dimensions, high risk of LVOT obstruction, etc.)
5. Anatomically prohibitive mitral annular calcification (MAC)
6. Aortic valve disease requiring intervention or previous intervention within 90 days of enrollment
7. Severe tricuspid regurgitation
8. Patients unsuitable for implantation because of congenital abnormalities of the IVC, thrombosis of the femoral vein and/or of IVC, history of venous stents (iliac and/or femoral), presence of a vena cava filter or intracardiac mass or intracardiac thrombus
9. Right-sided congestive heart failure with echocardiographic evidence of severe right ventricular dysfunction
10. Pulmonary hypertension with resting pulmonary artery systolic pressures ≥2/3 systemic pressure
11. Left ventricular ejection fraction (LVEF) <30%
12. Left ventricular end diastolic diameter (LVEDD) > 75mm
13. Hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, or other structural heart disease causing heart failure other than dilated ischemic or non-ischemic cardiomyopathy
14. Infiltrative cardiomyopathies (e.g., amyloidosis, hemochromatosis, sarcoidosis)
15. Subject is contraindicated for transesophageal echocardiography (TEE)
16. Need for emergent or urgent cardiac or non-cardiac surgery
17. Hemodynamic instability requiring dependency of either inotropic agents or mechanical circulatory support
18. Subject refuses a blood transfusion
19. Subject unwilling or unable to adhere to the protocol specified anticoagulation treatment
20. Blood dyscrasias as defined: leukopenia (WBC <1000 cells/mm3), thrombocytopenia (platelet count <50,000 cells/mm3)
21. History of bleeding diathesis or coagulopathy that precludes anticoagulation
22. Active gastrointestinal (GI) bleeding that would preclude anticoagulation
23. Known hypersensitivity or contraindication to nitinol, or sensitivity to contrast media which cannot be adequately pre-medicated
24. Any cardiac or peripheral interventional procedure performed within 30 days prior to enrollment in patients treated with bare-metal stent or drug-eluting stent (DES) with approved 1-month DAPT labeling or within 90 days prior to enrollment for subjects treated with DES without approved 1-month labeling.

25. Untreated clinically significant coronary artery disease requiring revascularization
26. Severe symptomatic carotid stenosis
27. Recent Stroke or TIA within 90 days of enrollment
28. Evidence of an acute myocardial infarction within 90 days prior to enrollment
29. Active endocarditis or active infection requiring antibiotic therapy
30. Implant of any Cardiac Resynchronization Therapy (CRT) or Cardiac Resynchronization Therapy with cardioverter-defibrillator (CRT-D) within 90 days of enrollment
31. End stage renal disease requiring chronic dialysis or creatinine clearance < 30 cc/min within 30 days of the Index Procedure
32. Severe Chronic Obstructive Pulmonary Disease (COPD) demonstrated by Forced Expiratory Volume (FEV1) < 750cc
33. Pregnancy, breastfeeding, or intent to become pregnant prior to completion of all protocol follow-up requirements
34. Currently participating in an investigational drug or another device study that has not yet reached its primary endpoint
35. Other medical, social, or psychological conditions that in the opinion of the Investigator precludes the subject from appropriate consent or adherence to the protocol required follow-up exams

9. Study Procedures

9.1 Schedule of Events

All enrolled subjects will undergo in-clinic follow-up evaluations through at least 5 years. A schedule of events is outlined below in Table 2. Upon completion of the final protocol visit (discontinuation) subject participation will be considered complete and the patient should then be followed per the local standard of care for their condition.

Table 2: Schedule of Events Table

	Screening & Baseline	Pre-Index Procedure	Index Procedure	Discharge	1 Month	3 Months	6 Months	12 Months	Every 6 Months through 5 Years
Informed consent	X								
Inclusion/Exclusion	X	X							
Demographics & Medical History	X								
Physical Examination	X			X	X	X	X	X	X
NYHA	X				X	X	X	X	X
Frailty Assessments & KATZ	X								
Pregnancy Test	X[1]								
Modified Rankin Scale (mRS)	X[2]								
Laboratory Tests[3, 4]	X			X	X	X	X	X	X
Transthoracic Echocardiogram (TTE)	X	X[5]		X[6]	X[6]	X[6]	X[6]	X[6]	X[6]
Transesophageal Echocardiogram (TEE)	X		X						
Right Heart Catheterization	X	X[7]							
MDCT	X[8]			X[9]				X[9]	
Coronary Arteriogram	X								
12-lead ECG	X			X	X	X	X	X	X
6 Minute Walk Test[12]	X				X	X	X	X	X
Quality of Live Questionnaire(s) QoL[11]	X				X	X	X	X	X
Adverse Events & Device Deficiencies			X[10]	X	X	X	X	X	X
Medications	X	X		X	X	X	X	X	X
Heart Failure Management	X	X	X	X	X	X	X	X	X

1. If female and child-bearing age
2. mRS is required to be collected at screening and conducted at 30 and 90 days following any stroke or TIA event, as applicable
3. B-type Natriuretic Peptide (BNP) or NT-proBNP, along with Creatinine, CBC and Albumin required at follow-up visits
4. INR levels to be monitored and reported for all subjects receiving warfarin anticoagulation therapy
5. TTE with limited views is required within 7 days of the Index Procedure to assess cardiac status (i.e. cardiac index, LVEF, PA pressure and mitral regurgitation)
6. If clinically necessary, or at Investigator discretion, TEE is to be conducted in addition to TTE to further evaluate any potential clinically significant findings during the follow-up period
7. Right heart catheterization may be used to supplement TTE measurements, as applicable
8. Complete visualization of femoral veins and inferior vena cava up to and including the mitral annulus
9. Subjects declining the MDCT at time of follow-up or unable to have the assessment will not be considered a protocol deviation
10. Adverse events collected after the subject is enrolled in the study.

11. Quality of Life Questionnaires collected at baseline (Minnesota Living with Heart Failure Questionnaire, SF-12 and KCCQ)may be administered any time after the subject has been approved for enrollment
12. Subjects physically unable to complete the 6MWT assessment will not be considered protocol deviations

9.2 Data Collection

The investigator must ensure accuracy, completeness and timeliness of the data reported in the EDC system and in all other required reports. Data reported on the CRFs which are derived from source documents must be consistent with the source documents or the discrepancies need to be justified in a documented rationale, signed and dated by the (principal) investigator, and are to be filed in the subject file.

Required data will be recorded on the CRFs by authorized site personnel as indicated on the Delegation of Authority Log. The CRFs 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 CRF.

The EDC system maintains an audit trail on entries, changes, or corrections in CRFs. If a person only authorized to complete CRFs makes changes to an already signed CRF, the investigator shall re-sign this CRF.

No trial document or image is permitted to be destroyed without prior written agreement between the Sponsor and the investigator. If the investigator wishes to assign the trial records to another party or move them to another location, advance written notice must be provided to the Sponsor. See Section 15.8 - Record Retention for additional requirements.

9.3 Scheduled Follow-up Visit Windows

After receiving notice of successful index procedure, Medtronic will provide the target dates and windows for each visit to the study site, if applicable. Should a subject miss a visit or the visit falls outside the pre-specified window, a study deviation must be reported and the original follow-up schedule maintained for subsequent visits.

Data analyses include follow-up visits, regardless of whether the visit occurs within the window. Therefore, a late visit is preferred over a missed visit but must be accompanied by a protocol deviation. Follow-up visit windows are listed in Table 3 and are based on days post-implant.

Table 3: Study Visit Windows

Study Visit	Visit Window	
	Target (days post-implant)	Window (days post-implant)
1 Month	30	±14
3 Month	90	±14
6 Month	183	±14

1 Year	365	±30
18 Month	548	±30
2 Year	730	±30
30 Month	913	±30
3 Year	1095	±30
42 Month	1278	±30
4 Year	1460	±30
54 Month	1643	±30
5 Year	1825	±30

9.4 Subject 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 IRB and by Medtronic. 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. The ICF 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. Where applicable, ICF certified translations are permitted when in compliance with local IRB requirements and approved by Medtronic.

Prior to the patient or legally authorized representative signing the ICF, the investigator or authorized delegate will fully explain to the patient or legally authorized 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 legally authorized 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 legally authorized representative, the patient or legally authorized 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 and a signed copy of the informed consent will be provided to the patient or legally authorized representative.

In the event the subject or legally authorized representative cannot read and/or write, the ICF process shall be obtained through a supervised oral process. An independent and impartial witness must be present during this process. The ICF and any other information must be read aloud to the prospective subject or his/her legally designated representative. Whenever possible, either the subject or his/her legally authorized representative shall sign and personally date the informed consent form. The witness signs and personally dates the ICF attesting that the information was accurately explained, and that informed consent was freely given.

Medtronic will inform the investigators whenever information becomes available that may be relevant to the subject's continued participation in the study. The revised information will be sent to the investigator for approval by the IRB. After approval by the IRB, a copy of this information must be provided to each participating subject, and the informed consent process as described above needs to

be repeated. The investigator or his/her authorized delegate should inform the subject in a timely manner.

The ICF template will be provided under separate cover.

9.5 Subject Screening

Standard examinations and tests, which are typically performed for patients undergoing similar procedures such as conventional mitral valve surgery, minimally invasive mitral valve repair (e.g., MitraClip), or Transcatheter Aortic Valve Implantation (TAVI) will be used both to screen eligible patients and provide baseline information for those patients that meet study criteria.

The process of screening and subject enrollment is as follows:

1. Patients identified by or presented to the trial site with mitral regurgitation will be screened by the investigative team for the criteria described in Section 8 – Selection of Subjects, using available medical records, including list of comorbidities, current medical management and relevant imaging studies previously performed for diagnostic purposes.
2. If the patient is deemed a potential candidate for the trial, the investigational status of the Intrepid™ TMVR System and all aspects of the trial will be explained to the patient. The patient will then be invited to participate in the trial.
3. If the patient agrees to participate, written informed consent will be obtained and the patient will be assigned a Study ID number.
4. The patient will undergo screening evaluations not previously conducted as standard of care.
5. Local Heart Team assessment of eligibility for enrollment

Clinical assessment including:

6. Proposed enrollment within the EFS
7. Evaluation of heart failure management including device therapy and assessment of guideline directed medical therapy
8. Anatomical assessment including:
    a. Anatomic suitability for the Intrepid™ valve
    b. Anatomic suitability and access for the Intrepid ™ TMVR Delivery System
9. If the local Heart Team considers the subject anatomically suitable for implantation and eligible for enrollment, the patients' clinical information will be submitted to the Screening Committee. The Heart Team assessment must be documented. The following information should be submitted to the Screening Committee:
    - Clinical assessments including STS-PROM, medical history, medications, heart failure management & co-morbidities,
    - Demographic & Medical History
    - Physical Examination (inclusive of vital signs, height, weight, & NYHA Class)
    - Frailty Assessments (Frailty Toolset & KATZ Index of Independence)

- Pregnancy Test (If female and child-bearing age)
- Coronary Arteriogram
- Right heart catheterization
- 12-lead Electrocardiogram (ECG)
- Lab tests
    - Creatinine
    - Complete Blood Count (CBC)
    - Albumin
    - B-type Natriuretic Peptide (BNP) or NT-proBNP
    - INR, if applicable (INR levels to be monitored and reported for all subjects receiving warfarin anticoagulation therapy)
- Resting TEE and TTE data on degree of mitral regurgitation
- Multidetector Computed Tomography (MDCT) data on anatomical suitability including complete visualization of femoral veins and inferior vena cava up to and including the Mitral valve annulus

The Screening Committee will review the clinical information to confirm the eligibility of the patient for enrollment and implantation. Screening Committee approval must be obtained for the subject to move forward in the study.

Written informed consent must be obtained prior to undergoing any protocol-required testing. If any of protocol-required screening evaluations (e.g., echocardiography, MDCT, coronary arteriography, lab work) have been performed for clinical diagnostic purposes prior to study consent, existing data/results may be used to satisfy the protocol-required exams, provided they contain the required information.

All subjects who are considered for the study should be documented on the study screening log. The reasons for non-eligibility, as determined by the Investigator should be recorded on the study Enrollment and Screening Log. The screening log serves as a method for Medtronic to assess selection bias in the trial.

9.6 Additional Screening Assessments

Additional screening assessments will be obtained for subjects that are deemed as anatomically suitable. The evaluations include:

- Modified Rankin Score (mRS)
- 6-Minute walk test (6MWT)
- Quality of Life (QOL) Questionnaires – Minnesota Living with Heart Failure Questionnaire, SF-12 and KCCQ

Subjects physically unable to complete the 6MWT assessment will not be considered protocol deviations. The mRS assessment will occur at screening for all subjects, and is required to be conducted at 30 and 90 days following any stroke or transient ischemic attack (TIA) that occurs during the study period.

9.7 Pre-Index Procedure

Cardiac status is required to be assessed for all subjects to confirm it is appropriate to proceed with the Index Procedure (i.e., subject has not decompensated since screening committee review). Assessment must be completed within one (1) to 7 days prior to the Index Procedure. Key cardiac assessments via TTE will be evaluated, at minimum: cardiac index, LVEF, pulmonary artery (PA) pressure and tricuspid regurgitation. A right heart catheterization may be used to supplement TTE measurements, as applicable.

Subject status must be assessed to confirm the subject continues to meet all the inclusion criteria and none of the exclusion criteria by local heart team. Current Medications and Heart Failure management will be assessed and collected at this visit.

9.8 Enrollment

Enrollment will only occur after confirmation that the patient meets all inclusion criteria, does not meet any exclusion criteria, has been assessed by the Heart Team as being an appropriate candidate for enrollment and approved by the Screening Committee. A subject is considered enrolled into the study once the subject is documented as enrolled in the Oracle Electronic Data Capture (EDC) database system following a successful Pre-Index Procedure. The date that this is completed in Oracle EDC begins the Adverse Event reporting timeline for that subject.

9.9 Index Procedure

The Intrepid™ TMVR procedure requires meticulous preparation and typically a multi-disciplinary team approach involving among others, interventional cardiologists, cardiac imaging specialists, cardio-thoracic surgeons and anesthesiologists.

The implant procedure itself takes place either in a hybrid suite or an operating room equipped for state-of-the-art transcatheter and/or surgical procedures. Procedural adverse event and device deficiency collection will be assessed throughout, as applicable and heart failure management will be collected.

The execution of the TMVR procedure involves an operating team typically consisting of a minimum of 2 operators (one managing the delivery catheter and another managing the inflation device) and an echocardiographer. Members of the implant team must be study investigators for the site and meet the minimum qualifications as outlined in section 7.4. The Fourth Position TMVR Procedure role will be completed by a delegated study team member who has completed the case debrief training for intended procedure at that site and is activated as a sub-I on the study. Additional case support functions may include an anesthesia team and nurses/technicians. Medtronic representative(s) (e.g.,

Therapy Development Specialists, proctors, etc.) may be present during TMVR procedures for training purposes, to perform valve loading and/or to provide general case support.

Device preparation, subject preparation and the implant procedure are to be completed in accordance with the Instructions for Use found in section 17.3.

Note: Closure of the atrial septal defect (ASD) created for transseptal crossing of the delivery system is recommended at the completion of implantation for all subjects treated.

No concomitant procedures are permitted during the index TMVR procedure. Any occurrence will be deemed a protocol deviation.

At the conclusion of the TMVR procedure, the following is assessed via TEE:

- Cardiac function including MR grade
- Paravalvular leak
- Atrial septal defect (ASD) as applicable

9.10 Discharge

Subjects will be cared for through discharge according to standard procedures for mitral valve replacement surgery.

Antithrombotic medication is recommended to be initiated in accordance with local practice and no earlier than Day 1 post-operatively. The recommended post-implant regimen for all subjects is dual anticoagulation/antiplatelet therapy for a minimum of 6 months with a target INR of 2.5. Dual warfarin and aspirin (81mg) are recommended.

It is also recommended that deep vein thrombosis (DVT) prophylaxis be administered in accordance with local practice for any subject treated, until the INR reaches therapeutic level.

Prior to discharge (or within 14 days post procedure whichever comes first), the following standard exams and tests will be performed:

- Physical exam and review of adverse events and device deficiencies
- Heart Failure Management & Medications
- TTE (addition of TEE evaluation if deemed clinically necessary, or at Investigator discretion)
- 12-lead ECG
- Laboratory tests
  - Creatinine
  - Complete Blood Count
  - Albumin
  - B-type Natriuretic Peptide (BNP) or NT-proBNP

  - INR, if applicable (INR levels to be monitored and reported for all subjects receiving warfarin anticoagulation therapy)
- Multidetector Computed Tomography (MDCT)

  Subjects declining the MDCT at time of follow-up or unable to have the assessment will not be considered a protocol deviation

9.11 Scheduled Follow-up Visits

Scheduled visits will occur at 1, 3, 6 months (± 2 weeks), at 12 months and every 6 months (± 30 days) through 5 years.

The following information is required to be collected at follow-up visits:

- Physical exam (including NYHA Class) and review of adverse events and device deficiencies
- Heart Failure Management & Medications
- 6-minute walk test (6MWT)
- TTE (addition of TEE evaluation if deemed clinically necessary, or at Investigator discretion)
- 12-lead ECG
- Laboratory tests:
  - Creatinine
  - Complete Blood Count
  - Albumin
  - B-type Natriuretic Peptide (BNP) or NT-proBNP
  - INR, if applicable (INR levels to be monitored and reported for all subjects receiving warfarin anticoagulation therapy)
- QoL surveys: Minnesota Living with Heart Failure Questionnaire, SF-12 and KCCQ
- Multidetector Computed Tomography (MDCT)[2] (12-month visit only)

Note: If a subject's TMVR implant is replaced with surgical replacement valve, the subject will be followed through 1-month post-surgical replacement.

Any unscheduled visits if deemed appropriate per physician discretion would be captured in the Unscheduled visit CRF. Data collected at an unscheduled visit would reflect similar follow-up visit assessments such as subject current status, NYHA Classification, medications, healthcare utilization, and echocardiography parameters as available. If this visit is associated with an Adverse Event, the information will be instead captured in the appropriate AE CRF entry as applicable.

9.12 Stroke Evaluation

Modified Rankin Score (mRS) assessment is required to be conducted at 30 and 90 days following any new suspected stroke or TIA event during the study period.

[2] Subjects unable to have the CT assessment will not be considered a protocol deviation.

9.13 Healthcare Utilization

Health Care Utilization information will be collected at any new hospital admission (excluding the Index Procedure admission). Health Care Utilization to be collected includes facility type and location as well as the start and end date of healthcare utilization facility.

9.14 Quality of Life (QoL) Questionnaires

Quality of Life questionnaires used in this protocol include Minnesota Living with Heart Failure Questionnaire, SF-12 and KCCQ

9.15 Prior and Concomitant Medications

During subject screening, heart failure medications will be reviewed by the local Heart Failure Specialist and Screening Committee to evaluate the patient's current medication regimen. It is recommended that patients with heart failure are on optimal guideline-directed medical therapy; if not, recommendations may be made by the Screening Committee to optimize medical therapy.

Subjects on existing antithrombotic regimens may be required to discontinue current medications at the discretion of the local Heart Team for either the Index Procedure and/or in favor of alternative/preferred regimens post-procedure.

Please refer to Section 9.10 Discharge for post-procedure medication recommendations.

9.16 Assessment of Efficacy

The following methods will be used for assessing, recording, and analyzing efficacy. Refer to Section 9.1 Schedule of Events for timing of these assessments.

- Heart team assessment
- MDCT
- TTE and TEE
- NYHA functional classification
- Quality of life questionnaires

9.17 Assessment of Safety

All adverse events and device deficiencies will be collected from the time of enrollment until the end of the study or until study exit, whichever comes first.

The safety assessment performed during this study will be based on the relatedness to the TMVR implant and index procedure.

9.18 Recording Data

Data entered must be traceable to source documents. Source documentation is defined as the first time data appear, and may include original documents, data, and records (e.g., hospital records, clinical and office charts, procedure reports, laboratory notes, memoranda, or evaluation checklists, X-rays, subject

files, device data and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the study).

In general, eCRFs (or paper copies) may not serve as source documents. An exception may be the completion of QoL Questionnaires. Source documentation for data elements not routinely captured in medical records may vary from study site to study site; the study site may use source document worksheets if identified as source documents.

The investigator must ensure the availability of source documents from which the information on the eCRFs was derived. The type and location of source documents should be documented. Where printouts of electronic medical records, are provided as source documents, or where copies of source documents are retained as source documents, those should be certified. Certification must contain (1) the signature of the individual making the copy, (2) the date the copy was made and (3) a statement attesting to the accuracy and completeness of the copy.

The source documents must be made available for monitoring or auditing by Medtronic's representative or representatives of the competent authorities and other applicable regulatory agencies.

9.19 Deviation Handling

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 unless specified within the protocol.

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/EC protocol review and approval before starting the trial
- Enrollment of patient during an IRB/EC 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 or USADE 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.

FDA regulations [21 CFR 812.150], the latest version of ISO 14155, and local regulatory authorities (where applicable), require Investigators to obtain prior approval from the sponsor before initiating changes in or deviations from the protocol, except when necessary to protect the rights, 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. If approval is granted, the Medtronic trial manager or designee will provide the applicable documentation to be maintained in the site files.

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

- A deviation from protocol to protect the life or physical wellbeing of a patient in an emergency
- Failure to obtain an informed consent

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

Repetitive or serious investigator compliance issues may represent a need to initiate a corrective action plan with the investigator and trial site, and in some cases, terminating the investigator's participation in the trial.

The Data Monitoring Committee (DMC) may review protocol deviations to ensure compliance and overall study integrity.

9.20 Subject Exit, Withdrawal or Discontinuation

All subjects will be encouraged to remain in the trial through the last follow-up visit applicable as listed in Section 9.3. Subjects who discontinue participation prematurely will be included in the analysis of results (as appropriate) and will not be replaced in the enrollment of total trial subjects. If a subject is discontinued from the trial early, the reason for discontinuation is to be documented in the subject file and a Trial Exit CRF must be completed.

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

9.20.1 Study Completed

At the completion of the 5-Year follow-up visit, subjects will be exited from the study.

9.20.2 Lost to Follow-up

A subject will not be considered lost to follow-up unless all efforts to obtain compliance are unsuccessful. At a minimum, the effort to obtain follow-up information must include 3 documented attempts to make contact via telephone and if contact via phone is not successful, a traceable letter from the investigator is to be sent to the subject's last known address. If both telephone and mail efforts to contact the subject are unsuccessful, the subject's primary physician is to be contacted, per the subject's informed consent. Subjects will then be deemed lost to follow up. All contact efforts to obtain follow-up must be documented in the subject's medical records. Subjects will not be replaced.

9.20.3 Subject Death

In the event that a subject dies after implantation of the TMVR bioprosthesis, the Investigator will make reasonable effort to have an autopsy performed to help determine the extent to which the subject's death was related to the device/procedure. If possible, the TMVR bioprosthesis will be explanted and returned to the Sponsor. Contact your Medtronic representative to obtain instructions for proper return of the device.

9.20.4 Subject Chooses to Exit (i.e. Revokes Consent)

A subject can withdraw from the study at any time. If the subject wishes to exit from the study (i.e. the subject revokes consent), the study site is required to document the reason for exit on the Exit CRF. In addition, study sites shall follow the regulations set forth by the IRB. Reason for exit must be documented.

9.20.5 Investigator Withdraws Subject

No subjects should be withdrawn by investigators unless compelling medical justification is present. It is recommended investigators discuss any withdrawals with the study team prior to withdrawing subjects. If an Investigator Withdrawal is necessary, the reason for withdrawal must be documented.

10. Risks and Benefits

10.1 Potential Risks

The potential risks associated with the investigational TMVR procedure are similar to the risks of cardiac surgery and mitral valve replacement. These risks may include, but are not limited to, the following risks:

- Death
- Cardiac damage or perforation, cardiac tamponade or pericardial effusion
- Coronary artery perforation, spasm, occlusion or obstruction
- Heart rhythm disturbances (e.g., atrial fibrillation, cardiac arrest)
- Conduction system disturbances (e.g., atrioventricular node block, left-bundle branch block, asystole), which may require a permanent pacemaker
- Aortic valve dysfunction (e.g., regurgitation or stenosis)
- Myocardial infarction, ischemia or angina
- Reduced cardiac function or continuing or worsening heart failure
- Stroke or transient ischemic attack (TIA)
- Encephalopathy / neurological deficit
- Renal insufficiency or failure (possibly requiring dialysis)
- Pulmonary complications (e.g., pulmonary congestion, hypertension, thromboembolism, dyspnea, respiratory failure, atelectasis, pneumonia)
- Surgical incision site complications (e.g., infection, inflammation, bleeding, hemothorax, hematoma, pain, irreversible nerve injury, wound dehiscence)

- Bleeding (possibly requiring a transfusion or other intervention)
- Emboli (air, thrombus)
- Infection (e.g., at incision sites, endocarditis, septicemia)
- Viral infection including Bovine Spongiform Encephalopathy (BSE)
- Blood abnormality (e.g., coagulopathy, hemolysis, anemia)
- Allergic or drug reaction (e.g., to anesthetic, contrast, Heparin, protamine, nickel alloy, latex)
- Esophageal complications due to transesophageal echocardiography (e.g., irritation, perforation, stricture)
- Tracheal complications due to intubation (e.g., irritation, perforation, dysphagia)
- Vascular access site complications (e.g., trauma, dissection, perforation, infection, inflammation, pain, bleeding, hematoma, pseudoaneurysm, irreversible nerve injury, compartment syndrome, arteriovenous fistula, stenosis)
- Aortic complications (for example, trauma, dissection, perforation, tears, aneurysm, pseudoaneurysm, or occlusion)
- Other systemic effects or symptoms (e.g., abnormal lab values, electrolyte imbalance, fever, hyperthermia, hypotension, hypertension, syncope, nausea, vomiting, edema, deep vein thrombosis, pleural effusion, lymphatic complications, urinary tract infection, multi-system organ failure, gastrointestinal bleeding, ischemia or infarction)
- Valve implant dysfunction (e.g., fracture, bending, under-expansion, suture breaks, calcification, pannus, thrombus, inflammation, stenosis, leaflet wear, tear, prolapse, retraction, poor valve coaptation, leaks, regurgitation, mal-sizing [prosthesis-patient mismatch])

The risks of the investigational TMVR procedure are similar to the surgical risks listed above; however, some may be increased with the TMVR procedure or implant. For example, the risks of cardiac damage may be increased by the TMVR delivery procedure, and the risk of valve implant dysfunction (as compared to surgical replacement valves) has not yet been established.

In addition to the risks listed above, the potential risks associated with the TMVR procedure and the Intrepid TMVR System may include, but are not limited to, the following risks:

- Valve implant detachment, migration, malposition, and/or incorrect sizing
- Injury to mitral valve apparatus complicating or preventing later surgical repair/replacement
- Left ventricular outflow tract (LVOT) obstruction
- Emergent surgical or transcatheter intervention (for example, coronary artery bypass, heart valve replacement or repair, transcatheter valve explant, percutaneous coronary intervention [PCI], balloon valvuloplasty, transcatheter valve or component retrieval)
- Failure to deliver the bioprosthesis to the intended site
- Failure to retrieve the system components
- Delivery system component embolization
- Delivery system thrombosis

- Prolonged cardiopulmonary bypass
- Prolonged ventilation, anesthesia, and/or procedure time
- Radiation skin burn or tissue reaction
- ASD with or without intervention
- Deep venous thrombus (DVT)
- Dislodgement of previously implanted devices (e.g., Dislodgement of lead in patient with pre-existing permanent pacemaker, CRT-P,CRT-D or implantable defibrillator (ICD))
- Edema
- Gastrointestinal bleeding or infarct
- Hypotension/hypertension
- Lymphatic complications
- Mesenteric ischemia
- Mitral stenosis
- Multisystem organ failure
- Nausea/vomiting
- Peripheral ischemia
- Respiratory failure/atelectasis/pneumonia
- Urinary tract infection
- Vessel spasm
- Worsening heart failure

The likelihood of these risks is unknown, as this is the initial introduction of the investigational TMVR system into a human population. However, bench-top testing and animal studies have demonstrated that the TMVR procedure can safely and reliably result in stable positioning of The Intrepid TMVR implant and the desired improvement in hemodynamic performance.

There may be other, as yet unknown, complications that may occur as a result of this procedure. If these or any of the above complications occur, they may lead to repeat or prolonged hospitalization, repeat procedures, emergency surgery, other emergency procedures, or in rare cases, death. The study doctor and/or his research staff will make every effort to minimize additional risks.

10.2 Risk Minimization

The potential risks associated with the Intrepid™ TMVR System were identified and have been mitigated to the extent possible. Any potential risks associated with this study are further minimized by selecting qualified investigators and training study personnel on the CIP. Medtronic has also attempted to minimize risk to subjects implementing a DMC to review safety issues as part of the study.

In addition, investigators will be actively involved in the implantation and follow-up of the subjects implanted with the Intrepid™ TMVR Systems.

Risks will be minimized by careful assessment of each subject prior to, during, and after implant of the Intrepid™ TMVR valve. Prior to implant, it is recommended subjects undergo a complete physical evaluation.

Medtronic has further minimized the possibility of risks by performing required laboratory and pre-clinical testing prior to this early feasibility study, implementing quality control measures into production processes, providing guidelines for subject selection and evaluation, and providing adequate instructions and labeling.

After implantation, subjects in this early feasibility study will be followed at regular intervals to monitor the condition of the implanted system. At each protocol required follow-up, the investigator must evaluate the Intrepid™ TMVR valve via TTE to verify appropriate valve function and to assess any adverse events.

10.3 Potential Benefits

Subjects who are eligible for this study suffer from moderate-severe or severe, symptomatic mitral regurgitation that requires definitive treatment. A participant may benefit from replacement of the mitral valve for treatment of mitral regurgitation. The potential benefits may include a reduction of mitral regurgitation and the possible health improvements and/or symptom relief associated with that reduction in mitral regurgitation.

There may be no direct benefit associated to participation in this trial, but the information obtained during this trial will be used scientifically to help physicians understand the implications of transcatheter treatment of the patient's mitral regurgitation.

10.4 Risk-Benefit Rationale

This early feasibility study will enroll only patients with moderate-severe or severe, symptomatic mitral regurgitation, who are ineligible for conventional mitral valve surgery. These patients, nevertheless, require treatment. This less invasive TMVR procedure may provide an alternative mitral valve replacement for patients for whom conventional surgery is not an option. Transfemoral transseptal access may also mitigate procedural complications compared to transapical access from the TMVR procedure.

The human clinical experience, to date, has demonstrated successful implantation of the Intrepid TMVR system, proper TMVR function, and elimination of mitral regurgitation, warranting continued study in additional patients, as proposed in this study. The potential benefit of a less invasive transseptal procedure to reduce their mitral regurgitation is considered to outweigh the risks from a MVR surgical procedure or a transcatheter valve replacement via transapical approach.

The investigational plan is specifically designed to manage and minimize risks through careful patient 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.

Study subjects will be exposed to the procedural and device risks associated with TMVR, as well as the study specific risks listed in Section 10.1. However, evidence from the scientific literature indicates subjects with moderate-to-severe or severe mitral regurgitation who do not receive therapy are exposed to the serious risks associated with their disease including worsening heart failure, irreversible ventricular functional impairment, and death.

While the Intrepid TMVR System is a novel device, based on the results of the Pilot Study and the benefits observed by relieving mitral regurgitation in other transcatheter mitral valve repair and replacement trials, it is expected that these benefits will be conferred to the study subjects in the Mitral Early Feasibility Study, and that the benefit of mitral regurgitation reduction will outweigh the risks of intervention.

In addition, an independent DMC will monitor safety of the subjects throughout the trial.

Therefore, the risk/benefit ratio for the study is justified.

10.5 Risk Determination

The devices used in this study are considered significant risk per 21 CFR 812.

11. Adverse Events and Device Deficiencies

11.1 Adverse Events

Adverse Event (AE) definitions are provided in 11.4 Table 4. All subject AE information will be collected throughout the study duration, starting at the time of enrollment.

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

For AEs that require immediate reporting (see 11.5, Table 6), initial reporting may be done on the CRF by completing as much information as possible. The completed AE CRF must be submitted to Medtronic as soon as possible.

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

Subject deaths are also required to be reported.

11.2 Device Deficiency

Device deficiency information will be collected throughout the trial and reported to Medtronic. Device deficiencies that led to an AE are reported on the AE CRF. Device deficiencies that did not lead to an AE are to be reported on a Device Deficiency CRF (one for each device deficiency).

Device deficiencies will be assessed for SADE potential. Device deficiencies that did not lead to an adverse event but might have led to a SADE if:

- a suitable action had not been taken, or
- an intervention had not been made, or
- circumstances had been less fortunate,

Device deficiencies are to be reported to Medtronic as soon as possible, but no later than three (3) working days after the investigator first learns of the event.

11.3 Processing Updates and Resolution

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

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

11.4 Definitions/Classifications

The definitions to be applied for the purposes of reporting adverse events are provided in Table 4.

Table 4: Adverse Event and Device Deficiency Definitions and Reporting Requirements

Event Type	Definition
Adverse Event (AE) (ISO14155:2020 3.2)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other parties, whether or not related to the investigational medical device and whether anticipated or unanticipated. *NOTE: This definition includes events related to the investigational medical device or the comparator.* *NOTE: This definition includes events related to the procedures involved.* *NOTE: For users or other persons, this definition is restricted to events related to investigational medical devices or comparators.*
Serious Adverse Event (SAE) (ISO14155:2020 3.45)	Adverse event that led to any of the following: a) death, b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following: 1) life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, including chronic diseases, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) foetal distress, foetal death or a congenital abnormality or birth defect including physical or mental impairment

	NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event. *The interpretation of Seriousness will exclude certain interventions considered standard of care during hospitalization (e.g., IV hydration, certain medications delivered intravenously due to available intravenous access or NPO (nothing by mouth) status, and the delivery of electrolytes to maintain electrolyte balance or to address mild electrolyte depletion). Any non-oral medication or fluid delivery used to treat an acute physical decompensation/deterioration episode or to otherwise resuscitate a subject will be considered serious by definition in that it prevents a permanent impairment of a body structure or deterioration of the health of a subject.
Adverse Device Effect (ADE) (ISO14155:2020 3.1)	Adverse event related to the use of an investigational medical device. Note: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation or any malfunction of the investigational medical device. Note: this definition includes any event resulting from use error or from intentional misuse of the investigation medical device. Note: this includes 'comparator' if the comparator is a medical device.
Serious Adverse Device Effect (SADE) (ISO14155:2020 3.44)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) (21 CFR 812.3)	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 investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE) (ISO14155:2020 3.51)	Serious adverse device effect (SADE) which by its nature, incidence, severity or outcome has not been identified in the current risk assessment. Note: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.
Device Deficiency (ISO 14155-:2020 3.19)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. Note: Includes malfunctions, user errors, and inadequacy in the information supplied by the manufacturer including labelling. Note: This definition includes device deficiencies related to the investigational medical device or the comparator
Serious Health Threat (ISO 14155:2020 3.46)	A signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. Note: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

Unavoidable events are conditions which do not fulfill the definition of an Adverse Event, such as those medical occurrences, clinical signs (including abnormal laboratory findings), diseases or injuries that are not untoward in nature, specifically, those resulting from the intended injury such as the index

procedure. The events listed in Table 5 are expected for patients undergoing the Index Procedure, and do not need to be reported as an AE unless they occur outside of the stated timeframe, are otherwise considered to be an AE according to the treating investigator or are suspected or confirmed to be device-related.

Table 5: Non-reportable Medical Occurrences Associated with the Index Procedure

Event	Timeframe (hours) from the Index Procedure
Short transient episode of arrhythmias or conduction disturbances (including ventricular fibrillation) during index procedure	0
Confusion, anxiety and/or disorientation (other than TIA/stroke) starting within 48 hours with or without medical intervention	120 (5 days)
Temporary change in mental status (other than TIA/stroke) not requiring additional medical interventions or new medical assessments (eg, CT)	72
Dizziness and/or lightheadedness with or without treatment	24
Headache with or without treatment	72
Sleep problems or insomnia with or without treatment	120 (5 days)
Mild dyspnea or cough with or without treatment	72
Oxygen supply after extubation / "forced breathing therapy"	48
Diarrhea with or without treatment	48
Obstipation / Constipation with or without treatment	72
Anesthesia-related nausea and/or vomiting with or without treatment	24
Low-grade fever (<101.3°F or <38.5°C) without confirmed infection	48
Low body temperature	6
Pain (eg, back, shoulder) related to laying on the procedure table with or without treatment	72

Incisional pain (pain at access site) with or without standard treatment and patient not returning to clinic to have additional treatment	No time limit
Pain in throat and/or trachea due to intubation	72
Stress hyperglycemia	72
Mild to moderate bruising or ecchymosis	168 (7 days)
Atelectasis / Pleural Effusion not requiring punctuation	168 (7 days)
Edema resulting in weight increase up to 4 kg / 9lbs from baseline	168 (7 days)

11.5 Reporting of Adverse Events

Adverse events and device deficiencies that occur during this trial are required to be reported to Medtronic via the AE or Device Deficiency CRF, as soon as possible after the event occurs, but no later than the timeframes listed in Table 6 or local requirements, whichever is more stringent.

Investigators are obligated to report adverse events in accordance with the requirements of their reviewing IRB and local regulations.

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

Table 6: Adverse Event Reporting Timelines [Investigator to Sponsor]

Event Type	Timeframe for Reporting
Adverse Event (AE)	Recommended within 10 working days of the investigator's / site's first knowledge of the event
Serious Adverse Event (SAE)	Immediately, but no later than three (3) working days of the investigator's / site's first knowledge of the event
Adverse Device Effect (ADE) or Device Related Adverse Event	Immediately, but no later than three (3) working days of the investigator's / site's first knowledge of the event
Serious Adverse Device Effect (SADE)	Immediately, but no later than three (3) working days of the investigator's / site's first knowledge of the event
Unanticipated Adverse Device Effect (UADE)	Immediately, but no later than three (3) working days of the investigator's / site's first knowledge of the event
Unanticipated Serious Adverse Device Effect (USADE)	Immediately, but no later than three (3) working days of the investigator's / site's first knowledge of the event

Event Type	Timeframe for Reporting
Device Deficiency	Immediately, but no later than three (3) working days of the investigator's / site's first knowledge of the event
Device Deficiency that might have led to a SADE	Immediately, but no later than three (3) working days of the investigator's / site's first knowledge of the event
Mandatory Problem Reporting Incident (Canada ONLY)	Immediately, but no later than three (3) working days of the investigator's / site's first knowledge of the event

Emergency Contact Details for Reporting SAE, SADE, UADE, and Device Deficiencies

Investigators should contact their designated Medtronic representative or clinical trial monitor immediately if they have any questions regarding reportable AEs. Medtronic will provide sites with a copy and maintain a listing of current sponsor contact details, inclusive of safety reporting.

11.5.1 Adverse Event and Device Deficiency Classification

All AEs and DDs will be reviewed by a Medtronic representative. AEs will be classified according to the definitions provided.

Upon receipt of AE at Medtronic, a Medtronic representative will review the AE/DD for completeness and accuracy and when necessary will request clarification and/or additional information from the Investigator. Source documents to support adjudication may be requested. Medtronic will utilize MedDRA for Regulatory Activities, to assign a MedDRA term for each AE based on the information provided by the investigator.

Regulatory reporting of AEs and DDs will be completed according to local regulatory requirements. Refer to Table 7 for a list of required investigator and Medtronic reporting requirements and timeframes. It is the responsibility of both to abide by any additional AE reporting requirements stipulated by the IRB responsible for oversight of the study.

For emergency contact regarding a UADE, USADE, SAE and/or SADE, contact a study representative immediately (refer to the study contact list provided in the study site's study documents binder).

AEs and Deaths will be classified according to the standard definitions as outlined below:

Table 7: Adverse Event Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	Classifying causal relationships between the event and the Intrepid™ TMVR bioprosthesis (TMVR), delivery catheter system (DCS), Loading System, and the TMVR procedure.
	Sponsor	Classifying causal relationships between the event and the Intrepid™ TMVR bioprosthesis (TMVR), delivery catheter system (DCS), Loading System and the TMVR procedure.
Seriousness	Investigator	SAE, DD with SADE potential
	Sponsor	SAE, UADE/USADE (for all system or procedure related adverse events), DD with SADE potential
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator

11.5.2 Adverse Event and Device Deficiency Reporting Requirements

Regulatory reporting of AEs and DDs will be recorded and reported according to local regulatory requirements. It is the responsibility of the Investigator and the sponsor to abide by the AE reporting requirements stipulated by local law and the study site's IRB. Refer to section 15.8.1 and 15.8.2 for reporting requirement.

11.6 Subject Death

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

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

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

In summary, the following data will be collected:

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

11.6.1 Death Classification and Reporting

Sufficient information will be required in order to properly classify the subject's death.

For all deaths, investigators must assess and document the following information on the Study Exit CRF

- Date of death
- Primary death category

Table 8: Subject death classification responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	Classifying causal relationships between the event and the Intrepid™ TMVR bioprosthesis (TMVR), delivery catheter system (DCS), loading system, and the TMVR procedure.
Death Classification	Investigator	Sudden Cardiac, Non-sudden Cardiac, Non-cardiac, Unknown

The CEC will review deaths and provide a final adjudication of the primary cause of death and classification of death.

Regulatory reporting of Subject Deaths will be completed according to local regulatory requirements.

12. Data Review Committees

12.1 Clinical Events Committee Review

An independent Clinical Events Committee (CEC) will review and adjudicate, at a minimum, all deaths and primary endpoint related adverse events. The CEC will consist of, at a minimum: an interventional cardiologist, a cardiothoracic surgeon, an echocardiologist and a heart failure specialist who are not participants in the trial. Additional specialists, such as neurologists, may also be selected as part of the CEC.

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 trial protocol and the CEC charter, which will be developed and approved by Medtronic and the CEC members. Safety endpoint results will be based on CEC adjudication.

All applicable events will be reviewed and adjudicated by a minimum of three CEC members. All other events will be reviewed and assessed by qualified internal Medtronic safety individual(s) to ensure that adjudication by the CEC is not required and that the events are appropriately classified by the investigator.

Prior to event adjudication, the CEC will draft a charter, in collaboration with Medtronic, to 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 master file and adjudication results will be recorded in the trial database.

12.2 CRO/Core Lab(s)

This information may be subject to change during the course of the study. Periodic updates to study contact information will be sent to study sites as needed.

Table 9: CRO and Core Laboratory Information

Contact Information	Role
Baim Institute for Clinical Research 930 Commonwealth Ave 3rd Floor Boston, MA 02215	Clinical Events Committee (CEC) / Data Safety Monitoring Committee (DSMB)
Mayo Clinic Core Laboratory 200 First Street SW Rochester, MN 55905e.g. Echocardiography Core Laboratory	Echocardiography Core Laboratory:
CVPath Institute, Inc. 19 Firstfield Road Gaithersburg, MD 20878	Explanted Device/Pathology Core Laboratory
Medidata Solutions, Inc. 350 Hudson Street 9th Floor New York, NY 10014	Medidata Solutions, Inc. (imaging sharing network)

12.3 Data Monitoring Committee

An independent, unblinded Data Monitoring Committee (DMC) also referred to as a Data Safety Monitoring Board (DSMB) will be established and will be comprised of at least 4 members with one biostatistician and 3 physicians, including a chairperson. The DMC/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 nor will Investigators be permitted to participate in closed sessions. Medtronic personnel may facilitate the DMC/DSMB meeting but will not have voting privileges nor attend closed sessions.

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

The DMC/DSMB will meet on a periodic basis to perform a comprehensive data review and will also perform a supplemental review of, at a minimum, all serious adverse events and deaths and any other data requested by the DMC/DSMB to ensure patient safety. DMC/DSMB members will provide recommendations about the conduct of the study (e.g., 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 or USADEs, if Medtronic and the DMC/DSMB determine that the event presents an unreasonable risk to the participating subjects, Medtronic must terminate the clinical trial within 5 working days after making that determination and 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.

Additional details about the DMC/DSMB are outlined in the DMC/DSMB charter.

13. Statistical Design and Methods

The objectives of this prospective, non-randomized Early Feasibility Study are to evaluate the safety and performance of The Intrepid™ TMVR System. A comprehensive analysis of the feasibility study results, as a whole, will be assessed to evaluate the overall risk/benefit balance for the patient population being treated. In addition, the following endpoints will be assessed and reported:

Primary safety endpoint:

- Implant, delivery or device related serious adverse events (through 30 days post-procedure)

Secondary performance endpoints:

- Successful access, delivery of implant, and retrieval of the delivery system
- Reduction in MR Grade from baseline (measured by echo through 30 days post-procedure)
- No significant MV stenosis (measured by echo through 30 days post-procedure)
- Change in NYHA Class from baseline (through 30 days post-procedure)

Additional exploratory endpoints:

- Measured by echocardiography post-procedure through 5 years:
  - Reduction in MR Grade from baseline
  - No significant MV stenosis
  - LV outflow tract (LVOT) patency
  - Improvement in LVEF
  - Improvement in cardiac output/cardiac index
  - Reduction in LV end-systolic and end-diastolic dimensions
- Presence of intra-atrial shunt with clinically significant pressure gradient requiring closure device
- Change in NYHA Class from baseline through 5 years
- Change in 6MWT from baseline through 5 years
- Change in QoL from baseline through 5 years
- Procedural times (e.g., deployment time, access duration, rapid pacing duration)
- Re-hospitalizations for heart failure
- MVARC1 defined outcomes of:
  - Technical success upon exit from operating room
  - Device success at 30 days and 1 year
  - Procedural success at 30 days
  - Individual subject success at 1 year

Event and endpoint definitions for this study's analysis will be based on those definitions outlined in the MVARC Consensus (9). Each subject's data will be reviewed individually and event summaries for all subjects will be provided to FDA. The data analysis will include all subjects who undergo the TMVR procedure and all available follow-up data (e.g., key echocardiographic measures and clinical status) at each post-procedure interval.

Mitral regurgitation will be classified according to the Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A report from the American Society of Echocardiography developed in Collaboration with the Society of Cardiovascular Magnetic Resonance; JASE, 2017 as outlined in Appendix 17.1:Definition of Terms & Causal Relationships .

The sample size is based upon industry standards for early feasibility stage studies of medical devices; the sample size was not statistically derived, as this is not a hypothesis-testing study.

13.1 General Aspects of Analysis

The analysis sets used for each objective are defined in the Statistical Analysis Plan. Study results will be summarized using standard descriptive statistics. Pre-defined statistical "success" or "pass" criteria for the study endpoints are not applicable for this feasibility study, as it is not a powered, hypothesis driven study. Baseline demographic and clinical variables will be summarized. Continuous variables will be

summarized with means, standard deviations, medians, interquartile ranges, minimums, and maximums. Categorical variables will be summarized with frequencies and percentages.

For each of the objectives the available data will be summarized. Number of subjects with available data will be presented so that the impact of missing data can be evaluated. The main analysis of the study objectives will be based on available data and missing data will not be imputed.

14. Ethics

14.1 Statement(s) of Compliance

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

In the United States, the study will be conducted under a Food and Drug Administration (FDA) Investigational Device Exemption (IDE) in compliance with FDA Code of Federal Regulations (CFR):

- 21 CFR Part 11: Electronic Records, Electronic Signatures
- 21 CFR Part 50: Protection of Human Subjects
- 21 CFR Part 54: Financial Disclosure by Clinical Investigators
- 21 CFR Part 56: Institutional Review Boards
- 21 CFR Part 812: Investigational Device Exemptions
- The latest version of ISO 14155

This study will be publicly registered prior to first enrollment in accordance with the 2007 Food and Drug Administration Amendments Act (FDAAA) and Declaration of Helsinki on 41T41TUUhttp://clinicaltrials.govUU41T41T (PL110-85, Section 810(a)).

ISO14155:2020 Deviations

The Mitral Early Feasibility Study design includes three deviations from ISO14155:2020. The first is the time of enrollment which is defined as the date the clinical site indicated "enrolled" within Oracle Clinical, following Screening Committee approval, as opposed to the date of consent. Given the expected high screen failure rate this was done to reduce the burden of unnecessary assessments on subjects and reduce the burden of adverse event reporting by sites that would not be utilized in analyses. The second deviation is due to the fact that the study is an early feasibility study and therefore does not have statistically powered endpoints due to the purpose of the study. The third deviation from ISO is due to no non-subject AEs collected for this study, as these are not of interest in this study.

15. Study Administration

15.1 Monitoring

It is the responsibility of Medtronic to ensure proper monitoring of this study. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring at the study site in order to ensure that the study is conducted in accordance with the CIP, the CTA, and the applicable regulatory and local requirements. Medtronic, or delegates, must therefore be allowed direct access to the subjects' case histories (clinic and hospital records, and other source data/documentation) upon request as per the ICF and CTA. The principal investigator should also be available during monitoring visits.

15.1.1 Monitoring Visits

Frequency of monitoring visits may be based upon subject enrollment, study compliance, number of adverse events, number of deviations, observations from previous monitoring visits and any suspected inconsistency in data that requires investigation. Regulatory documents may be reviewed at each study site. Monitoring for the study, including site initiation visits, interim monitoring visits, and closeout visits, will be done in accordance to the study-specific monitoring plan.

The investigational site will be monitored to assess study site progress (per the monitoring plan), ensure compliance with the trial protocol, adherence to applicable regulations, and accuracy of trial data. Monitoring visits will be conducted primarily to ensure the rights, safety and wellbeing of the subjects is preserved. Monitoring visits will also be used to verify that trial data submitted on case report forms (CRF) are complete and accurate with respect to the subject records and to verify device accountability.

The Investigator(s), their delegate(s) and the study coordinator(s) shall be accessible during monitoring visits. Accessibility is of particular importance for reviewing data in the CRF.

Site personnel will complete CRFs 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 be conducted via a risk-based approach as outlined in the Monitoring Plan.

The progress of the trial will be monitored according to the Monitoring Plan by:

- On-site/Remote review, as deemed appropriate by the sponsor
- Centralized review, as deemed appropriate by the sponsor
- Essential communications between the site personnel (e.g., Investigator, Trial Coordinator) and trial monitors
- Review of CRFs and the associated clinical records
- Review of regulatory documents
- Review of Subject Informed Consent(s)
- Review of Device Accountability Logs
- Review of equipment maintenance and calibration documentation

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

Monitoring and monitoring oversight will be provided by Medtronic, Inc. Representatives of the study sponsor (e.g., contractors and designees) may also act as the trial monitors to the site. Medtronic will maintain an updated list of applicable representatives and provide a copy to sites upon request.

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

15.2 Data Management

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

All records and other information about subjects participating in this study will be treated as confidential. Data will be transferred and processed by Medtronic or a third party designated by Medtronic in a key coded form, unless it's impossible to pseudonymize for instance, where the subject's name cannot be removed from the data carrier, such as Echocardiogram images. The investigational study site team will upload images (e.g., Echocardiogram, ECG, CT) to Medidata Solutions as source data to be retrieved by the imaging core lab for review. Procedures in the CIP require source documentation. Source documentation will be maintained at the study site. Source documents, which may include worksheets and subject medical records must be created and maintained by the investigational study site team.

The investigator will clearly mark clinical records to indicate that the subject is enrolled in this clinical investigation.

The data reported on the CRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing.

15.3 Direct Access to Source Data/Documents

The investigator and/or institution shall permit Medtronic, IRBs and regulatory bodies direct access to source data and documents during monitoring, audits and regulatory inspections.

15.4 Audits

Medtronic may conduct audits at participating study sites. The purpose of an audit is to verify the performance of the monitoring process and the study conduct, independently of the personnel directly involved in the study. Regulatory bodies such as the FDA, may also perform inspections at participating study sites.

15.5 Confidentiality

All information and data sent to parties involved in study conduct concerning subjects or their participation in this study will be considered confidential. Study sites will assign a unique subject number to each subject. Records of the subject/subject number relationship will be maintained by the study site. The subject number is to be recorded on all study documents to link them to the subject's medical records at the study site. Confidentiality of data will be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data. In the US, "Protected Health Information" (PHI) will be maintained in compliance with the HIPAA of 1996. To maintain confidentiality, the subject's name or any other PHI should not be recorded on any study document other than the ICF. This scenario will be covered in the ICF. In the event a subject's name/PHI is included for any reason, it will be blinded as applicable. In the event of inability to blind the identification (e.g., digital media), it will be handled in a confidential manner by the authorized personnel. Data relating to the study might be made available to third parties (for example in case of an audit performed by a regulatory body), provided the data are treated as confidential and that the subject's privacy is guaranteed. No identifiable subject information will be published.

15.6 Liability/Warranty/Insurance Information

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

15.7 CIP Amendments

Revisions to the Clinical Investigation Plan will be managed per Medtronic's standard operating procedures. Medtronic will submit amendments to the CIP, including a justification for the amendment, to all affected regulatory agencies and to the investigators to obtain approval from their IRB, as applicable. The investigator will only implement the amendment after approval of the IRB, regulatory agencies, and Medtronic.

15.8 Record Retention

The investigator must retain all study-related documents for a period of at least 2 years after market-release in his/her region and after study closure (or longer if required by local law). Medtronic will inform the investigator/study site when these documents are no longer required to be retained.

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

Medtronic will retain the study records according to Medtronic corporate policy and record retention schedule.

15.8.1 Investigator Records

The investigator is responsible for the preparation and retention of the records cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the

Investigator Site File (i.e., the study binder provided to the investigator) or Subject Study Binder. CRFs must be maintained and signed electronically within the electronic data capture system during the study. The following records are subject to inspection and must be retained as noted above in Section 15.8.

- 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/device deficiency 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 CIP, including the date and the rationale for such deviation
- Signed Investigator Agreement, signed and dated curriculum vitae of the PI, sub-investigator(s) and key members, signed Delegated Task List
- The approved CIP, Patient Information/Informed Consent Form, Investigator Brochure or Report of Prior Investigations, and any amendments
- Insurance certificate, where applicable
- IRB/EC Approval documentation and voting list
- Regulatory authority notification and approval documentation
- List of sponsor contacts and monitoring contact list
- List of investigation sites
- Training records
- Disclosure of conflict of interest
- Lab certificate/lab normal ranges
- Subject ID and enrollment log
- Sponsor's interim analyses and clinical investigation report

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 in Table 10 and Table 11, for their respective geographies. These are also subject to inspection by government agencies and must be retained. Reports will be submitted to regulatory authorities per local reporting requirements/regulations. Requirements for reporting Adverse Events to Medtronic are described in Table 6.

15.8.2 Sponsor Records

Medtronic shall maintain the following accurate, complete, and current records including but not limited to:

- All essential correspondence which pertains to the investigation
- Investigational device traceability record containing Model and serial numbers of devices, shipping date and name and address of person that received shipped device, location (if different than person shipped to), transfer and receipt by Medtronic dates.>
- Sample of label attached to investigational device
- Signed and dated clinical trial agreement for each investigation study site
- Signed investigator agreements, financial disclosure and current CV of principal investigators
- Delegated task list for each investigation study site
- All approved ICF templates, and other information provided to the subjects and advertisements, including translations
- Copies of all IRB approval letters and relevant IRB correspondence and IRB voting list/roster/letter of assurance
- Names of the institutions in which the study will be conducted
- FDA correspondence, notification and approval as required by national legislation
- Names/contact addresses of monitors
- Device complaint documentation
- Monitoring visit reports
- Statistical analyses and underlying supporting data
- Final report of the study
- The CIP, Investigator Brochure/Report of Prior Investigations summary and study related reports, and revisions
- Study training records for study site personnel and Medtronic personnel involved in the study
- Any other records that local regulatory agencies require to be maintained.

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

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

15.9 Reporting Requirements

15.9.1 Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events and adverse device effects, device deficiencies, deaths, and any deviations from the clinical investigation plan. If any action is taken by an IRB with respect to this study,

copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

Safety data investigator reporting requirements are listed in Section 11.5. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

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

Report	Submit to	Description/Constraints
Withdrawal of IRB approval (either suspension or termination)	Sponsor	An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation. (21 CFR 812.150(a)(2)).
Progress report	Sponsor and IRB	The investigator must submit this report to the sponsor and IRB at regular intervals, but in no event less than yearly. (21 CFR 812.150 (3)).
Study deviations	Sponsor and IRB	Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. (21 CFR 812.150(a)(4))
Failure to obtain IC prior to investigational device use	Sponsor and IRBs	If an investigator uses a device without obtaining informed consent, the investigator shall report such use within 5 working days after device use. (21 CFR 812.150(a)(5))
Final investigator report	Sponsor, IRB s and Relevant Authorities	This report must be submitted within 3 months of study completion or termination of the investigation or the investigator's part of the investigation. (21 CFR 812.150(a)(6))
Other	IRB and FDA	An investigator shall, upon request by a reviewing IRB, FDA or any other regulatory agency, provide accurate, complete, and current information about any aspect of the investigation. (21 CFR 812.150(a)(7))

15.9.2 Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the tables below (by geography). In addition to the reports listed below, Medtronic shall, upon request of

the reviewing IRB or FDA, provide accurate, complete and current information about any aspect of the investigation. Safety data Medtronic reporting requirements are listed in Table 11.

Table 11: Sponsor records and reporting responsibilities

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators, IRB Relevant authorities and Head of the Institution	Provide prompt notification of termination or suspension and reason(s). (ISO 14155:2020)
Unanticipated Adverse Device Effect	Investigators, IRB, FDA, and relevant authorities	Notification within ten working days after the sponsor first receives notice of the effect. (21 CFR 812.150(b)(1))
Withdrawal of IRB approval	Investigators, Head of Institution, IRB and relevant authorities	Investigators, IRBs will be notified only if required by local laws or by the IRB
Withdrawal of FDA approval	Investigators, Head of Institution, IRB, and relevant authorities	Notification within five working days after receipt of notice of the withdrawal of approval. (21 CFR 812.150(b)(3))
Investigator List	FDA	Submit at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. (21 CFR 812.150(b)(4))
Progress Reports	IRB and RAs	Progress reports will be submitted at least annually. (21 CFR 812.150(b)(4)(5), 812.36(f)
Recall and device disposition	Investigators, IRB, relevant authorities, and FDA	Notification within 30 working days after the request is made and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. (21 CFR 812.150(b)(6))
Failure to obtain Informed Consent	FDA	Investigator's report will be submitted to FDA within five working days of notification. (21 CFR 812.150(b)(8))

Report	Submit to	Description/Constraints
Final report	Investigators, IRB, Regulatory authorities, and FDA	Medtronic will notify FDA within 30 working days of the completion or termination of the investigation. A final report will be submitted to the FDA, investigators, and IRBs within six months after completion or termination of this study. (21 CFR 812.150(b)(7))
Study deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the CRFs and the final report of the clinical investigation. (ISO 14155:2020) Study site specific study deviations will be submitted to investigators periodically.

15.10 Publication and Use of Information

Medtronic is committed to the widespread dissemination of all primary and secondary endpoint results. A Publication Plan will be implemented and followed as indicated in the CTA.

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

15.11 Suspension or Early Termination

15.11.1 Planned Study Closure

Study Closure is a process initiated by distribution of a study closure letter. Study closure is defined as closure of a study that occurs when Medtronic and/or regulatory requirements have been satisfied per the CIP and/or by a decision by Medtronic or regulatory body), whichever occurs first. The study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. Ongoing IRB oversight is required until the overall study closure process is complete.

15.11.2 Early Termination or Suspension

Early Termination is the closure of a study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single study site. Suspension is a temporary postponement of study activities related to enrollment and distribution of the product. This is possible for the whole study or a single study site.

16. References

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7. Dvir D. Transseptal Instead of Transapical Valve Implantation. JACC: Cardiovascular Interventions 2016;9:1175-1177.
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17. Appendices

17.1 Definition of Terms & Causal Relationships

ACCESS SITE AND VASCULAR COMPLICATIONS

Access and vascular complications will be defined and classified according to the Mitral Valve Academic Research Consortium (MVARC); Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions; JACC, 2015 (2).

Access Site and Vascular Complications
I. Vascular complications
A. Major access site vascular complications, including: i. Aortic dissection or aortic rupture, or ii. Access site-related† arterial or venous injury (dissection, stenosis, ischemia, arterial, or venous thrombosis including pulmonary emboli, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, retroperitoneal hematoma, atrial septal defect‡), irreversible nerve injury, or compartment syndrome resulting in death; hemodynamic compromise; life-threatening, extensive, or major bleeding (MVARC bleeding scale); visceral ischemia; or neurological impairment, or iii. Distal embolization (noncerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage, or iv. Unplanned endovascular or surgical interventions resulting in death; life-threatening, extensive, or major bleeding (MVARC bleeding scale); visceral ischemia; or neurological impairment
B. Minor access site vascular complications, including: i. Access site arterial or venous injury (dissection, stenosis, arterial, or venous thrombosis including pulmonary emboli, ischemia, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, retroperitoneal hematoma, atrial septal defect‡) not resulting in death; life-threatening, extensive, or major bleeding (MVARC scale); visceral ischemia; or neurological impairment, or ii. Distal embolization treated with embolectomy and/or thrombectomy not resulting in amputation or irreversible end-organ damage, or iii. Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication, or iv. Vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft)
II. Cardiac structural complications due to access-related issues
A. Major cardiac structural complications, including: i. Cardiac perforation* or pseudoaneurysm resulting in death, life-threatening bleeding, hemodynamic compromise, or tamponade, or requiring unplanned surgical or percutaneous intervention
B. Minor cardiac structural complications, including: i. Cardiac perforation* or pseudoaneurysm not meeting major criteria

* Including the left ventricle, left atrium, coronary sinus, right atrium, and right ventricle.

† May arise from the access procedure per se or complications from vascular closure devices.

‡ Meeting pre-specified criteria for a hemodynamically significant shunt, or requiring unplanned percutaneous or surgical closure.

ACUTE KIDNEY INJURY

Acute Kidney Injury (AKI) will be defined and classified according to the Mitral Valve Academic Research Consortium (MVARC); Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions; JACC, 2015 (2).

Definition and Stages of Acute Kidney Injury
Definition
Maximal changes in sCr from baseline to 7 days post-procedure
Stages
Stage 1 Increase in sCr to 150%–199% (1.50–1.99x increase vs. baseline), increase of ≥0.3 mg/dl (≥26.4 mmol/l) within 48 h, or urine output <0.5 ml/kg/h for ≥6 h but <12 h **Stage 2** Increase in sCr to 200%–299% (2.00–2.99x increase vs. baseline) or urine output <0.5 ml/kg/h for ≥12 h but <24 h **Stage 3** Increase in sCr to ≥300% (≥3.0x increase vs. baseline), sCr of ≥4.0 mg/dl (≥354 mmol/l) with an acute increase of ≥0.5 mg/dl (44 mmol/l), urine output <0.3 ml/kg/h for ≥24 h, or anuria for ≥12 h; patients receiving renal replacement therapy are considered stage 3 irrespective of other criteria

Adapted with permission from Kappetein et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: The Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol 2012;60: 1438–54.

AORTIC REGURGITATION

Aortic regurgitation will be classified according to the 2008 Focused Update Incorporated into the ACC/AHA 2006 Guidelines for the Management of Patients with Valvular Heart Disease; JACC, 2008.

Aortic Regurgitation			
	Mild	Moderate	Severe
Qualitative			
Angiographic grade	1+	2+	3-4+
Color Doppler jet width	Central jet, width less than 25% of LVOT	Greater than mild but no signs of severe AR	Central jet, width greater than 65% LVOT
Doppler vena contracta width (cm)	Less than 0.3	0.3–0.6	Greater than 0.6

Quantitative (cath or echo)			
Regurgitant volume (ml per beat)	Less than 30	30–59	Greater than or equal to 60
Regurgitant fraction (%)	Less than 30	30–49	Greater than or equal to 50
Regurgitant orifice area (cm2)	Less than 0.10	0.10–0.29	Greater than or equal to 0.30
Additional essential criteria			
Left ventricular size	--	--	Increased

AORTIC STENOSIS

Aortic stenosis will be classified according to the 2008 Focused Update Incorporated into the ACC/AHA 2006 Guidelines for the Management of Patients with Valvular Heart Disease; JACC, 2008.

Aortic Stenosis			
Indicator	**Mild**	**Moderate**	**Severe**
Jet velocity (m/s)	Less than 3.0	3.0–4.0	Greater than 4.0
Mean gradient (mmHg)*	Less than 25	25–40	Greater than 40
Valve area (cm^2)	Greater than 1.5	1.0–1.5	Less than 1.0
Valve area index (cm^2 / m^2)	--	--	Less than 0.6

* Valve gradients are flow dependent and when used as estimates of severity of valve stenosis should be assessed with knowledge of cardiac output or forward flow across the valve. Modified from the Journal of the American Society of Echocardiography, 16, Zoghbi WA, Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography, 777–802, Copyright 2003, with permission from American Society of Echocardiography (33).

ARRHYTHMIAS AND CONDUCTION SYSTEM DISTURBANCES

Arrhythmias and conduction system disturbances will be defined and classified according to the Mitral Valve Academic Research Consortium (MVARC); Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions; JACC, 2015 (2).

Arrhythmias and Conduction System Disturbances
For emerging mitral valve procedures in which the frequency of major arrhythmias and conduction system disturbances is unknown, continuous rhythm monitoring for at least 48 h in the post-procedural period is recommended to maximize the detection of arrhythmias and conduction system disturbances.

Arrhythmias and Conduction System Disturbances
Data elements to be collected for all patients should include: I. Baseline conduction abnormalities, paroxysmal or permanent atrial fibrillation (or flutter), ventricular arrhythmias, and the presence of permanent pacemaker and implantable defibrillators* II. Procedure-related new or worsened cardiac conduction disturbance (including first-, second- [Mobitz I or Mobitz II], or third-degree AV block; incomplete and complete right bundle branch block; intraventricular conduction delay; left bundle branch block; left anterior fascicular block; or left posterior fascicular block, including heart block) requiring a permanent pacemaker implant; each subclassified as persistent or transient III. New-onset atrial fibrillation (or flutter)† IV. New-onset ventricular tachycardia or fibrillation V. Pacemaker or defibrillator lead dislodgement Arrhythmias and conduction system disturbances are subclassified according to: I. The occurrence of hemodynamic instability II. Need for therapy including electrical/pharmacological cardioversion or initiation of a new medication (oral anticoagulation, rhythm, or rate control therapy) III. Need for new permanent pacemaker and/or defibrillator implantation, including the indication(s) and the number of days post-implant. For patients with defibrillators, the number of appropriate and inappropriate shocks should be recorded.

* The type of permanent pacemaker should be recorded (e.g., single vs. dual chamber, biventricular).

† Which lasts sufficiently long to be recorded on a 12-lead electrocardiogram, or at least 30 s on a rhythm strip.

AV = atrioventricular

BLEEDING COMPLICATIONS

Bleeding complications will be further defined and classified according to the Mitral Valve Academic Research Consortium (MVARC); Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions; JACC, 2015 (2).

Major bleeding will be defined as any bleeding event requiring transfusion of ≥4 U of whole blood or packed RBCs.

Definition of Bleeding Complications
MVARC Primary Bleeding Scale*
I. Minor Any overt,† actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that meets ≥1 of the following: requiring nonsurgical medical intervention by a health care professional; leading to hospitalization or increased level of care; prompting evaluation; or requires 1 or 2 U of whole blood or packed RBC transfusion and otherwise does not meet criteria for major, extensive, or life-threatening bleeding. **II. Major**

Definition of Bleeding Complications
Overt bleeding either associated with a drop in the hemoglobin of ≥3.0 g/dl‡ or requiring transfusion of ≥3 U of whole blood or packed RBCs AND does not meet criteria of life-threatening or extensive bleeding. **III. Extensive** Overt source of bleeding with drop in hemoglobin of ≥4 g/dl‡ or whole blood or packed RBC transfusion ≥4 U within any 24-h period, or bleeding with drop in hemoglobin of ≥6 g/dl‡ or whole blood or packed RBC transfusion ≥4 U (BARC type 3b) within 30 days of the procedure. **IV. Life-threatening** Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating surgery or intervention, or intramuscular with compartment syndrome OR bleeding causing hypovolemic shock or hypotension (systolic blood pressure <90 mm Hg lasting >30 min and not responding to volume resuscitation) or requiring significant doses of vasopressors or surgery. **V. Fatal** Bleeding adjudicated as being a proximate cause of death. Severe bleeding adjudicated as being a major contributing cause of a subsequent fatal complication, such as MI or cardiac arrest, is also considered fatal bleeding.
Modified BARC Bleeding Scale (Secondary Use)[§]
Type 0 No Bleeding. **Type 1** Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional. May include episodes leading to self-discontinuation of medical therapy by the patient without consulting a health care professional. **Type 2** Any overt,† actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet ≥1 of the following: requiring nonsurgical medical intervention by a health care professional, leading to hospitalization or increased level of care, or prompting evaluation. **Type 3a** • Overt* bleeding plus hemoglobin drop of 3 to <5 g/dl‡ (provided drop is related to bleed) • Any transfusion with overt bleeding **Type 3b** • Overt bleeding plus hemoglobin drop ≥5 g/dl‡ (provided drop is related to bleed) • Cardiac tamponade • Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) • Bleeding requiring IV vasoactive agents **Type 3c** • Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation but does include intraspinal bleeding) • Subcategories confirmed by autopsy, imaging, or lumbar puncture • Intraocular bleeding compromising vision **Type 4 (periprocedural)** • Perioperative intracranial bleeding ≤48 h

Definition of Bleeding Complications
• Reoperation after closure of incision site for the purpose of controlling bleeding • Transfusion of ≥5 U whole blood or packed RBCs within 48 h period of the index procedure • Chest tube output ≥2 l within 24 h period **Type 5a** Probable fatal bleeding. No autopsy or imaging confirmation but clinically suspicious. **Type 5b** Definite fatal bleeding. Overt bleeding, autopsy, or imaging confirmation.

* Modified with permission from VARC-2 (29).
† "Overt" bleeding is defined by any of the following criteria being met: Reoperation after closure of sternotomy for the purpose of controlling bleeding; chest tube output >2 l within any 24 h period, >350 ml within the first post-operative hour, ≥250 ml within the second post-operative hour, or >150 ml within the third post-operative hour; or visible bleeding from the vascular system either at or remote from the access/surgical site.
‡ Adjusted for the number of units of blood transfused (1 U packed red blood cells or whole blood is equivalent to 1 g/dl hemoglobin).
§ Modified from BARC.
BARC = Bleeding Academic Research Consortium; IV = intravenous; MVARC = Mitral Valve Academic Research Consortium; RBC = red blood cells; VARC = Valve Academic Research Consortium.

BUNDLE BRANCH BLOCK

ACC/AHA/HRS 2006 Key Data Elements and Definitions for Electrophysiological Studies and Procedures; A Report of the American College of Cardiology/ American Heart Association Task Force on Clinical Data Standards (ACC/AHA/HRS Writing Committee to Develop Data Standards on Electrophysiology); JACC, 2006.

Left Bundle Branch Block (LBBB)

- QRS duration 120 ms or longer
- Delayed onset of intrinsicoid deflection in 1, 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 intrinsicoid deflection in V1 and V2 >50 ms
- Broad, slurred S wave in 1, V5, and V6
- Secondary ST-T wave changes

CARDIAC STRUCTURAL COMPLICATION-NON-ACCESS SITE RELATED

- Major cardiac structural complications, including:

- Cardiac perforation* or pseudoaneurysm resulting in death, life-threatening bleeding, hemodynamic compromise, or tamponade, or requiring unplanned surgical or percutaneous intervention

- Minor cardiac structural complications, including:
  - Cardiac perforation* or pseudoaneurysm not meeting major criteria

*including the left ventricle, left atrium, coronary sinus, right atrium and right ventricle

CARDIAC PERFORATION

A laceration or tearing of the walls of the ventricles or atria of the heart; of the interatrial or interventricular septum; of the papillary muscles or chordae tendineae; or of the one of the valves of the heart.

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

Cardiogenic shock will be defined as modified from the 2017 AHA Scientific Statement: Contemporary Management of Cardiogenic Shock

Cardiac disorder that results in tissue hypoperfusion as supported by:

- Systolic BP<90 mmHg for ≥30 minutes
  OR
- Cardiac Index of ≤1.8 L/min/m^2 and PCWP ≥15mmHg
  OR
- Intervention with pharmacological or mechanical support to maintain systolic BP ≥90 mmHg[1];
  AND
- End-organ hypoperfusion documented by:
  - Urine output <30 mL/h^2, **or**
  - Cool extremities, **or**
  - Clinical pulmonary congestion, **or**
  - Altered mental status, **or**
  - Lactate >2.0 mmol/L

  OR
- Death

Timing will be characterized as pre-operative, intra-operative (in the operating room), or post-operative (operating room discharge through 30 days).

Notes:

- Excluding prophylactic use of pharmacological or mechanical support
- Unless directly attributed to another medical condition

CHRONIC RENAL INSUFFICIENCY

Kidney damage or glomerular filtration rate (GFR) <60 mL/min/1.73 m2 for ≥3 months.

Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine test or imaging studies.

CONVERSION TO OPEN MITRAL VALVE SURGERY DURING A TRANSCATHETER PROCEDURE

Conversion to open mitral valve surgery will be defined and classified according to the Mitral Valve Academic Research Consortium (MVARC); Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions; JACC, 2015 (2).

Subclassified as:

- Secondary to mitral valve apparatus damage or dysfunction, requiring surgical valve repair or replacement, or
- Secondary to procedural complications (such as cardiac perforation, removal of an embolized device, and so on)

CORONARY VESSEL COMPRESSION OR OBSTRUCTION

Coronary vessel compression or obstruction will be defined and classified according to the Mitral Valve Academic Research Consortium (MVARC); Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions; JACC, 2015 (2).

Angiographic evidence of any reduction in coronary artery luminal diameter or coronary sinus diameter due to either external compression, thrombosis, embolism, dissection, or other cause, subclassified as:

- Major (≥50% diameter stenosis) or minor (<50%)
- Symptomatic or not
- Requiring treatment or not
- Transient (intraprocedural only, resolved at procedure end) or persistent

DAMAGE TO THE NATIVE MITRAL VALVE APPARATUS

Damage to the native mitral valve apparatus will be defined and classified according to the Mitral Valve Academic Research Consortium (MVARC); Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions; JACC, 2015 (2).

- Chords

- Papillary muscles
- Leaflets
- Mitral annulus

DEEP WOUND INFECTION

Deep Wound Infection will be defined and classified according to The Society of Thoracic Surgeons' (STS) Online Risk Calculator: Risk Model and Variables – STS Adult Cardiac Surgery Database Version 2.81.

Deep sternal wound infection or mediastinitis (per CDC definition) diagnosed within 30 days of the operation or any time during the hospitalization for the Index Procedure.

DEVICE FRACTURE

Device fracture will be defined and classified according to the Mitral Valve Academic Research Consortium (MVARC); Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions; JACC, 2015 (2).

- Major: a break, tear, perforation, or other structural defect in the device (stent, housing, leaflet, arm, and so on) resulting in device failure, resulting in recurrent symptoms, or requiring reintervention, or
- Minor: a break, tear, perforation, or other structural defect in the device (stent, housing, leaflet, arm, and so on) not resulting in device failure, not resulting in recurrent symptoms, and not requiring reintervention

DEVICE MIGRATION AND MALPOSITIONING

- Device Malposition: Intrepid valve is deployed in a location other than intended
- Migration with incomplete detachment: after initially correct transcatheter implantation of the Intrepid valve at the level of the mitral valve annulus, the device moves towards left atrium or left ventricle but stays partially or completely attached to the annulus.
- Migration with complete detachment: after initially correct transcatheter implantation of the Intrepid valve at the level of the mitral valve annulus, the device moves towards left atrium or left ventricle and completely loses its contact with the annulus.

DEVICE THROMBUS

Device thrombus will be defined as any thrombus attached to or near an implanted valve and will be subclassified as:

- *Clinically significant valve thrombosis:* visualization of thrombus by echo or by MDCT (including HALT ≥ 50%) and evidence of arterial embolism or new/worsening heart failure.

- *Significant thrombosis without clinical sequelae:* visualization of thrombus by echo or by MDCT (including HALT ≥ 50%) in the absence of arterial embolism or new/worsening heart failure, meeting criteria of significant increase in mean gradient across the implant* and warranting initiation or intensification of systemic anticoagulation.

- *Subclinical thrombosis:* visualization of thrombus by echo or by MDCT (including HALT ≥ 50%) in the absence of arterial embolism or new/worsening heart failure and not meeting criteria of significant increase in mean gradient across the implant*.

If thrombus is discovered on the implant at autopsy, it will be considered *clinically significant with clinical sequelae* if there was evidence of arterial embolism or new/worsening heart failure diagnosed ante- or postmortem. In the absence of arterial embolism or new/worsening diagnosed ante- or postmortem, thrombosis will be considered *significant without clinical sequelae* if last available echo met criteria of significant increase in mean gradient across the implant* and *subclinical* if last available echo does not meet criteria of significant increase in mean gradient across the implant*.

*trans-mitral mean Δ≥6 mmHg AND ≥5 mmHg increase from discharge (10)

The definition of ***Worsening Heart Failure*** is related to the valve thrombosis events. For Heart Failure admissions, please refer to ***Hospitalization*** subclassified as Heart Failure.

Definition of Worsening Heart Failure*
Presence of both: **I. New or progressive symptoms/signs of decompensation heart failure** a. History i. Significant weight gain ii. Worsening dyspnea iii. Worsening fatigue b. Physical Examination i. Newly elevated jugular venous pressure ii. New cardiac S3 gallop rhythm iii. New pulmonary rales iv. New hepatic congestion v. New peripheral edema vi. New development of cool extremities **II. Unplanned intensification of decongestive therapy in response to progressive symptoms/signs of heart failure:**

Definition of Worsening Heart Failure*
a. Oral i. Increased dose of loop diuretic ii. Addition of thiazide diuretic to loop diuretic b. Intravenous administration of diuretic

* Mallick et al. PROSPECT Trial. J Am Coll Cardiol HF 2016;4:749–55

EMBOLISM (BLOOD CLOT)

- 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.

EMBOLISM (AIR)

Venous air embolism – a subset of gas embolism that occurs when gas is introduced into the venous system.
Arterial air embolism – a subset of gas embolism that occurs when gas is introduced into the arterial system.

- Symptomatic = With Clinical Sequelae – (e.g. signs and/or symptoms of hemodynamic instability. ischemia, respiratory failure and/or new neurologic deficit)
- Asymptomatic = Without clinical sequalae

ENCEPHALOPATHY

Altered mental state (e.g., seizures, delirium, confusion, hallucinations, dementia, coma, psychiatric episode, etc.).

ENDOCARDITIS

Endocarditis will be defined and classified according to the Mitral Valve Academic Research Consortium (MVARC); Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions; JACC, 2015 (2).

Any 1 of the following:

- Fulfillment of the modified Duke endocarditis criteria (described below), or
- Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriological studies during an operation or autopsy.

Should be further subclassified by organism, and early (<1 yr) vs. late (≥1 yr)

Modified Duke Criteria
Definite endocarditis according to the Modified Duke Criteria includes: • Histologic and/or microbiologic evidence of infection at surgery or autopsy, or • 2 major criteria, or • 1 major criteria or 3 minor criteria, or • 5 minor criteria Major and minor criteria are as follows:
Major Criteria

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

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

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

HEMOLYSIS

Hemolysis will be defined and classified according to the Mitral Valve Academic Research Consortium (MVARC); Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions; JACC, 2015 (2).The presence of anemia requiring transfusion plus decreased/absent haptoglobin and/or increased LDH levels; recommended, but not required, to be confirmed by a hematologist.

- Hemolysis will be further sub-classified to the following:
  - Hemolysis with PVL: The presence of anemia requiring transfusion plus decreased/absent haptoglobin and/or increased LDH levels and evidence of a Paravalvular leak on transesophageal or transthoracic echocardiography
  - Hemolysis without PVL: The presence of anemia requiring transfusion plus decreased haptoglobin/absent and/or increased LDH levels and no evidence of a Paravalvular leak on transesophageal or transthoracic echocardiography
    - (e.g. hemolysis due to other devices such as Impella, etc. would fall into this category)

HOSPITALIZATION

Hospitalization will be defined and classified according to the Mitral Valve Academic Research Consortium (MVARC); Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions; JACC, 2015 (2).

Heart Failure hospitalization will be defined and classified according to MVARC.

Definition and Classification of Hospitalization (or Rehospitalization)
Definition
Hospitalization is defined as admission to an inpatient unit or ward in the hospital for ≥24 h, including an emergency department stay. Hospitalizations planned for pre-existing conditions are excluded unless there is worsening of the baseline condition.
Hospitalization is further subclassified as:
I. Heart failure hospitalization: Both of the following additional criteria are present: i. Symptoms, signs and/or laboratory evidence of worsening heart failure[1] ii. Administration of intravenous or mechanical heart failure therapies[2]

Definition and Classification of Hospitalization (or Rehospitalization)
Patients hospitalized with heart failure are further subclassified as: IA. Primary (cardiac related) heart failure hospitalization IB. Secondary (noncardiac related) heart failure hospitalization II. Other cardiovascular hospitalization: such as for coronary artery disease, acute myocardial infarction, hypertension, cardiac arrhythmias, cardiomegaly, pericardial effusion, atherosclerosis, stroke, or peripheral vascular disease without qualifying heart failure III. Non-cardiovascular hospitalization: not due to heart failure or other cardiovascular causes, as defined above

1. The diagnosis of worsening heart failure is on the basis of: 1) symptoms of worsening heart failure such as increased dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue, decreased exercise tolerance, and/or history of weight gain; 2) physical examination evidence of worsening heart failure such as neck vein distention, the presence of a third heart sound, pulmonary rales, ascites or pedal edema, and/or hypotension or signs of worsening end-organ perfusion; and/or 3) diagnostic evidence of worsening heart failure such as radiographic pulmonary congestion, natriuretic peptide levels greater than the upper limit of normal in the absence of conditions known to affect these values (e.g., renal dysfunction, infection), arterial oxygen desaturation or increasing oxygen requirements, and/or acidosis. No single finding is necessarily diagnostic, and adjudication by the clinical events committee should be on the basis of all available clinical evidence, guided by the specifics of the protocol definition.
2. Examples of intravenous heart failure therapies contributing to this definition would include bolus or continuous infusion of loop diuretic agents; continuous infusion of vasodilators such as nitroglycerin, nitroprusside, or nesiritide; inotropic agents such as dobutamine; inodilators such as milrinone; beta agonists; and vasopressors such as dopamine, epinephrine, and norepinephrine. Also included would be other invasive or mechanical heart failure treatments such as ultrafiltration, cardiac resynchronization therapy, and hemodynamic assist devices including intra-aortic balloon counterpulsation or left ventricular (LV) or biventricular assist devices. Treatment with intravenous antiarrhythmic medications or electrical cardioversion and/or ablation in the absence of other intravenous or invasive heart failure treatments would not per se constitute criteria for heart failure hospitalization (but would qualify as a cardiovascular hospitalization). Similarly, a heart failure exacerbation that can be managed solely by augmentation of oral heart failure therapies does not meet the pre-defined criteria for heart failure hospitalization.

IATROGENIC ATRIAL SEPTAL DEFECT

Iatrogenic ASD will be defined and classified according to the Mitral Valve Academic Research Consortium (MVARC); Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions; JACC, 2015 (2).

- Major: significant left-to-right shunt (Qp:Qs ≥2:1) or symptomatic requiring the need for closure
- Minor: nonsignificant shunt that is still present at ≥6 months

INTERACTION WITH NON-MITRAL VALVE INTRACARDIAC STRUCTURES

Interaction with non-mitral- valve intracardiac structures will be classified as

- Left ventricular outflow tract obstruction:
  - Visual narrowing of the LVOT tract AND
  - Peak LVOT jet velocity ≥ 2.7 m/s (peak instantaneous gradient ≥30 mmHg) measured by CW Doppler under basal (resting) conditions or physiologically provoked (Valsalva maneuver or post premature ventricular contraction) AND

- An increment in peak LVOT gradient ≥10 mm Hg from baseline

- Additional notes and considerations:
  - LVOT obstruction will be considered severe if peak LVOT jet velocity ≥ 3.5 m/s (peak instantaneous gradient ≥50 mm Hg).
  -
  - **Non-severe**: Peak LVOT jet velocity greater than or equal to 2.7 ms/s to 3.4 m/s (peak instantaneous gradient ≥30 mm Hg
  - **Non-event:** Less than 2.7 m/s peak LVOT jet velocity
  - All cases with peak LVOT jet velocity ≥ 2.7 m/s (peak instantaneous gradient ≥30 mm Hg) measured by CW Doppler will be submitted to the CEC for adjudication.
  - AEs/SAEs related to *intraprocedural* increase in LVOT gradient will be submitted to the CEC for adjudication. Cases of intraprocedural LVOTO resulting into death or explant will be considered severe LVOTO.
  - Cases of LVOTO resulting into septal reduction therapy (alcohol septal ablation or septal myectomy) will be considered severe LVOTO.
  - Cases of LVOTO incidentally discovered by pathology will be assessed based on the last available peak LVOT jet velocity measured by CW Doppler; any attempt should be done to submit this last echo to the Echo Core Lab and to the CEC. Alternatively, the last follow-up echo Core Lab CW measurements will be used to define LVOTO.

Outflow Tract Gradient Severity Scale CW Doppler			
	Mild	**Moderate**	**Severe**
Velocity m/sec	≥2.7-3.1	3.2 - 3.4	≥3.5
Peak Gradient mmHg	≥30-39	40 - 49	≥50

- Aortic valve regurgitation (≥ moderate or 2+)
- Other

INTERACTION WITH PACEMAKER/CRT/ICD LEAD

- Lead Dislodgement: Radiographic, micro dislodgement, electrical or electrocardiographic evidence of electrode displacement from the original implant site or electrode displacement that adversely affects pacing and/or lead performance
- Failure to Sense/Undersensing (Cardiac): Intermittent or complete loss of sensing or failure to detect the intended intrinsic cardiac signals (atrial or ventricular) during non-blanking periods at programmed sensitivity settings.
- Failure to Capture (Cardiac):

- Intermittent: Intermittent or irregular failure to achieve cardiac stimulation (atrial or ventricular) at programmed output delivered outside of the cardiac refractory period at settings previously effective
- Sustained: Continuous failure to stimulate the heart with stimuli delivered outside of the cardiac refractory period at programmed setting previously effective

- Lead Fracture: Visual, electrical, and/or radiographic evidence of mechanical break within the lead conductor (includes connectors, coils and/or electrodes)
- Failure to Pace: lack of the pacer electrical output once the heart rate is below the programmed lower rate of the pacemaker.

MITRAL REGURGITATION

Mitral regurgitation will be classified according to the Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A report from the American Society of Echocardiography developed in Collaboration with the Society of Cardiovascular Magnetic Resonance; JASE, 2017.

Qualitative and Quantitative Parameters useful in Grading Mitral Regurgitation Severity			
	MR Severity*		
	Mild	**Moderate**	**Severe**
Structural Parameters			
MV morphology	**None or mild leaflet thickening** (e.g., mild thickening, calcifications or prolapse, mild tenting)	Moderate leaflet abnormality of moderate tenting	**Severe valve lesions** (primary: flail leaflet, ruptured papillary muscle, severe retraction, large perforation; secondary: severe tenting, poor leaflet coaptation)
LV and LA size†	Usually normal	Normal or mile dilated	Dilated‡
Qualitative Doppler			
Color flow jet area§	**Small, central, narrow, often brief**	Variable	Large central jet (>50% of LA) or eccentric wall-impinging jet of variable size
Flow convergence‖	**Not visible, transient or small**	Intermediate in size and duration	**Large throughout systole**
CWD jet	Faint/partial/parabolic	Dense but partial or parabolic	Holosystolic/dense/triangular

Qualitative and Quantitative Parameters useful in Grading Mitral Regurgitation Severity				
	MR Severity*			
	Mild	**Moderate**		**Severe**
Semiquantitative				
VCW(cm)	<0.3	Intermediate		≥ 0.7 (>0.8 for biplane)¶
Pulmonary vein flow#	Systolic dominance (may be blunted in LV dysfunction or AF)	Normal or systolic blunting#		Systolic flow reversal†
Mitral inflow**	**A-wave dominant**	Variable		E-wave dominant (>1.2 m/sec)
Quantitative††,‡‡				
EROA, 2D PISA (cm^2)	<0.20	0.20-0.29	0.30-0.39	≥ 0.40 (may be lower in secondary MR with elliptical ROA)
RVol (mL)	<30	30-44	45-59††	≥ 60 (may be lower in low flow conditions)
RF (%)	<30	30-39	40-49	≥ 50

ROA, Regurgitant orifice area.

Bolded qualitative and semiquantitative signs are considered specific for their MR grade.

* All parameters have limitations, and an integrated approach must be used that weighs the strength of each echocardiographic measurement. All signs and measures should be interpreted in an individualized manner that accounts for body size, sex, and all other patient characteristics.

† This pertains mostly to patients with primary MR.

‡ LV and LA can be within the ''normal'' range for patients with acute severe MR or with chronic severe MR who have small body size, particularly women, or with small LV size preceding the occurrence of MR

§ With Nyquist limit 50-70 cm/sec.

‖ Small flow convergence is usually <0.3 cm, and large is $ 1 cm at a Nyquist limit of 30-40 cm/sec.

¶ For average between apical two- and four-chamber views

Influenced by many other factors (LV diastolic function, atrial fibrillation, LA pressure).

** Most valid in patients >50 years old and is influenced by other causes of elevated LA pressure.

†† Discrepancies among EROA, RF, and RVol may arise in the setting of low or high flow states.

‡‡ Quantitative parameters can help subclassify the moderate regurgitation group.

MITRAL STENOSIS

Mitral stenosis will be classified according to the 2008 Focused Update Incorporated into the ACC/AHA 2006 Guidelines for the Management of Patients with Valvular Heart Disease; JACC, 2008.

Mitral Stenosis			
Indicator	**Mild**	**Moderate**	**Severe**
Mean gradient (mmHg)*	Less than 5	5–10	Greater than 10

Pulmonary artery systolic pressure (mmHg)	Less than 30	30–50	Greater than 50
Valve area (cm^2)	Greater than 1.5	1.0–1.5	Less than 1.0

* Valve gradients are flow dependent and when used as estimates of severity of valve stenosis should be assessed with knowledge of cardiac output or forward flow across the valve. Modified from the Journal of the American Society of Echocardiography, 16, Zoghbi WA, Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography, 777–802, Copyright 2003, with permission from American Society of Echocardiography.

MITRAL VALVE DYSFUNCTION

Mitral valve dysfunction will be classified according to the Mitral Valve Academic Research Consortium (MVARC); Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions; JACC, 2015 (2).

The device performs as intended without complication but does not adequately reduce the degree of MR (MR > moderate [2+], or fails to relieve or creates new mitral stenosis [EROA <1.5 cm2 or transmitral gradient ≥5 mm Hg]).

MORTALITY

Mortality will be classified according to the Mitral Valve Academic Research Consortium (MVARC); Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions; JACC, 2015 (2).

Classification of All-Cause Mortality
I. Cardiovascular vs. Noncardiovascular Mortality
A. Cardiovascular Mortality Any of the following contributing conditions: Heart failure (subclassified into left ventricular vs. right ventricular dysfunction) Myocardial infarction Major bleeding Thromboembolism Stroke Arrhythmia and conduction system disturbance Cardiovascular infection and sepsis (e.g., mediastinitis and endocarditis) Tamponade Sudden, unexpected death Other cardiovascular Device failure Death of unknown cause (adjudicated as cardiovascular) B. Noncardiovascular Mortality

Classification of All-Cause Mortality
I. Cardiovascular vs. Noncardiovascular Mortality
Any death in which the primary cause of death is clearly related to another condition: Noncardiovascular infection and sepsis (e.g., pneumonia) Renal failure Liver failure Cancer Trauma Homicide Suicide Other noncardiovascular
II. Periprocedural vs. Nonperiprocedural Mortality
Death is considered periprocedural if occurring within 30 days of the intervention or beyond 30 days in the patient not yet discharged

MYOCARDIAL INFARCTION

Myocardial infarction (MI) will be defined according to the Mitral Valve Academic Research Consortium (MVARC); Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions; JACC, 2015 (2).

Definition of MI After Transcatheter and Surgical Mitral Valve Replacement
I. Periprocedural MI (≤48 h after the index procedure)*†
A. In patients with normal baseline CK-MB (or cTn): The peak CK-MB measured within 48 h of the procedure rises to ≥10x the local laboratory ULN plus new ST-segment elevation or depression of ≥1 mm in ≥2 contiguous leads (measured 80 ms after the J-point), or to ≥5x ULN with new pathological Q waves in ≥2 contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and with a normal baseline cTn, a cTn (I or T) level measured within 48 h of the PCI rises to ≥70x the local laboratory ULN plus new ST-segment elevation or depression of ≥1 mm in ≥2 contiguous leads (measured 80 ms after the J-point), or ≥35_ ULN with new pathological Q waves in ≥2 contiguous leads or new persistent LBBB. B. In patients with elevated baseline CK-MB (or cTn): The CK-MB (or cTn) rises by an absolute increment greater than or equal to those levels recommended above from the most recent pre-procedure level plus, new ECG changes as described.
II. Spontaneous MI (>48 h after the index procedure)‡
Detection of rise and/or fall of cardiac biomarkers (preferably cTn) with at least 1 value above the 99th percentile URL (or ULN in the absence of URL) together with at least 1 of the following:

Definition of MI After Transcatheter and Surgical Mitral Valve Replacement
A. Symptoms of ischemia B. ECG changes indicative of new ischemia (new ST-segment or T-wave changes or new LBBB) or new pathological Q waves in ≥2 contiguous leads C. Imaging evidence of a new loss of viable myocardium or new wall motion abnormality
III. MI associated with sudden, unexpected cardiac death‡
Sudden cardiac death or cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST-segment elevation or new LBBB and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurs before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood
IV. Pathological findings of an acute myocardial infarction‡
The use of high sensitivity (hs)-troponins is recommended for diagnosis of type II (spontaneous) MI, but has not been studied for assessment of periprocedural MI. Standard troponin assays are therefore recommended for evaluation of type I MI.

* Periprocedural biomarker elevation >ULN not meeting the criteria for MI should be categorized as "myonecrosis not meeting MI criteria."

† Adapted from Moussa et al. (43).

‡ Adapted with permission from Thygesen et al. (39).

CK-MB = creatine kinase-MB; cTn = cardiac troponin; ECG = electrocardiogram; LBBB = left bundle branch block; MI = myocardial infarction; ULN = upper limit of normal; URL = upper reference limit.

NEUROLOGICAL EVENTS

Neurological Events will be defined and classified according to the Mitral Valve Academic Research Consortium (MVARC); Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions; JACC, 2015 (2).

Stroke and Transient Ischemic Attack: Diagnosis and Classification
Diagnostic Criteria
Acute episode of a focal or global neurological deficit with at least 1 of the following: A. Change in the level of consciousness B. Hemiplegia, hemiparesis, numbness, or sensory loss affecting 1 side of the body C. Dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke In addition, there is no other readily identifiable nonstroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences) as determined by or in conjunction with the designated neurologist*
The neurological event type classification

Stroke and Transient Ischemic Attack: Diagnosis and Classification
Stroke: duration of a focal or global neurological deficit ≥24 h OR <24 h if available neuroimaging documents a new intracranial or subarachnoid hemorrhage (hemorrhagic stroke) or central nervous system infarction (ischemic stroke) OR the neurological deficit results in death TIA: duration of a focal or global neurological deficit <24h and neuroimaging does not demonstrate new hemorrhage or infarct
Confirmation of the diagnosis of stroke or TIA requires at least 1 of the following
Neurologist or neurosurgical specialist, or Neuroimaging procedure (CT scan or brain MRI)
Stroke/TIA timing classification
Periprocedural if it occurs within 30 days of the intervention, or if beyond 30 days in the patient not yet discharged. A periprocedural stroke/TIA may be further considered immediate if it occurs within 24 h of the procedure or within 24 h of awakening from general anesthesia if beyond 24 h. Nonperiprocedural if it occurs beyond 30 days after the intervention and after the patient has been discharged.
Stroke/TIA etiology classification
Ischemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue Hemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage Undetermined: if there is insufficient information to allow categorization as ischemic or hemorrhagic
Stroke severity† is further classified as
Disabling stroke: an mRS score ≥2 at 90 days plus an increase in ≥1 mRS category from the pre-stroke baseline Nondisabling stroke: an mRS score <2 at 90 days or without an increase ≥1 mRS category from the pre-stroke baseline

* Patients with nonfocal global encephalopathy will not be reported as having had a stroke without unequivocal evidence of cerebral infarction based upon neuroimaging studies (CT scan or cerebral MRI).

† Modified Rankin scale (mRS) assessments should be made by qualified individuals (such as nurse practitioner, physician assistant, doctor of osteopathy, or medical doctor) according to a certification process (20,55,56).

CT = computed tomography; MRI = magnetic resonance imaging; TIA = transient ischemic attack

PARAVALVULAR LEAK

PVL will be defined and classified according to the Mitral Valve Academic Research Consortium (MVARC); Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions; JACC, 2015 (2).

- Major: moderate or severe (2þ, 3þ, or 4þ), or associated with hemolysis, or requiring intervention or surgery

- Minor: trace or mild (1þ), without hemolysis

PERICARDIAL EFFUSION

Pericardial effusion will be defined and classified as adapted from the Mitral Valve Academic Research Consortium (MVARC); Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions; JACC, 2015 (2).

- Major: leading to cardiac tamponade or requiring intervention or hospitalization
- Minor: not leading to cardiac tamponade and not requiring intervention

PROLONGED VENTILATION

Modified from The Society of Thoracic Surgeons' (STS) Online Risk Calculator: Risk Model and Variables – STS Adult Cardiac Surgery Database Version 2.81.

Prolonged postoperative pulmonary ventilation > 24.0 hours. (These hours include OR exit until extubation, plus any additional hours following re-intubation through 30 days or hospital discharge, whichever is longer.)

REOPERATION OR REINTERVENTION

Reoperation and reintervention will be defined as those events adjudicated as procedure or valve related.

Any cardiovascular surgical (reoperation) or percutaneous interventional (reintervention) procedure performed following the index procedure (discharge from the operating room). Reoperation and reintervention will be classified as procedure related (e.g. bleeding/tamponade, dissection), valve related (e.g. endocarditis, valve dysfunction, thrombosis), or for other cardiovascular reasons (e.g., coronary occlusion, VSD).

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 (e.g. 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

TRICUSPID REGURGITATION

Tricuspid regurgitation will be classified according to the 2008 Focused Update Incorporated into the ACC/AHA 2006 Guidelines for the Management of Patients with Valvular Heart Disease; JACC, 2008.

Severe tricuspid regurgitation: vena contracta width greater than 0.7cm and systolic reversal in hepatic veins.

UNPLANNED USE OF CARDIOPULMONARY BYPASS (CPB)

Modified from the Valve Academic Research Consortium (VARC)-2; Updated Standardized Endpoint Definitions for Transcatheter Aortic Valve Implantation (TAVI); 2012-10-09 (29).

Unplanned use of CPB for hemodynamic support at any time during the TMVR procedure.

Classification of Causality Relationships	
Not related	The event is due to an underlying or concurrent illness or effect of another device, drug or intervention and is not related to the investigational device or procedure.
Unlikely (remotely) to be related	The event's relationship to the investigational device or procedure, cannot be completely ruled out, but is unlikely, and an alternative etiology is more likely.
Possibly related	The event has a strong temporal relationship to the investigational device or procedure, and an alternative etiology is equally or less likely.
Probably related	The event has a strong temporal relationship to the use of the investigational device or procedure and another etiology is unlikely or significantly less likely.
Causal (Definite) relationship	The event can only be attributed to the use of the investigational device or procedure.
Not Assessable	The event's relationship to the use of the investigational device or procedure cannot be assessed.

17.2 Sample Informed Consent

Sample Informed Consent templates will be provided under separate cover.

17.3 Instructions for Use

Instructions for Use (IFU) will be provided under separate cover for each device configuration/system that will be made available for clinical investigation under this protocol. The relevant regulatory and local requirements (IRB, etc.) for investigation of each configuration will be met prior to use of that system under this protocol.

Transfemoral/Transeptal System:

Investigational Device Configuration	Model Numbers		IFU Reference
Intrepid™ Transcatheter Mitral Valve Replacement System (Recoverable)	Bioprosthesis	INTPDVL42F INTPDVL48F	LBL-0087
	Delivery System	INTPDTF42DS INTPDTF48DS	
	Loading System	INTPDTFLS	

18. Version History

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/Title
1.0	• 'Not Applicable, New Document'		NA	NA	Sonia Diaz de Leon, Clinical Research Manager

2.0	• Added reference to transseptal where applicable • Changed "patient" to "subject" for assessments completed post screening • Added inclusion criteria for subject's ineligibility for conventional mitral surgery and severity of mitral regurgitation • Added reference for STS predictive model for inclusion and exclusion criteria • Added assessment of ASD and PVL via TEE post procedure • Updated post procedure medication recommendation • Added no significant ASD requiring closure in exploratory endpoints • Added MR classification and definitions • Updated for consistent terminology for quality of life questionnaires • Updated the number of investigational sites from 6 to 10	Added for clarity and consistency prior to final site release		N/A as version 1.0 unreleased to sites	Sonia Diaz de Leon, Clinical Research Manager

3.0	• Updates made throughout for alignment with ISO14155
	• Correction of typographical errors and administrative updates throughout
	• Updated to 056 Clinical Investigational Plan template and amended the following sections:
	  • Glossary
	  • Rationale / basis for study design
	  • Trial training
	  • Packaging
		Updates made to align with recent pivotal trial updates in APOLLO for clinical program alignment, new clinical investigation plan study template, and for compliance with ISO14155. Additional updates made per recommendations by safety, medical advisory, quality, and clinical leadership.	Increased sample size and sites may impact timeline of primary endpoint analysis. Increased specificity to additional exploratory endpoint definitions and safety parameters to more	Informed Consent Template, Case Report Forms, Protocol training slides, Safety Plan, Monitoring Plan, Statistical Analysis Plan, Clinical Trial Agreements	Sarah Brown, Pr. Clinical Research Specialist

	• Intended population • Equipment • Product Use • Product training requirements • Product receipt and tracking • Product return • Subject enrollment • Required evaluations • Assessment of efficacy and safety • Source documents • Potential benefits • Audits • Confidentiality • Instructions for lost to follow-up and when subjects die in Subject Withdrawal and Discontinuation section • Increased sample size to 45 total subjects enrolled at up to 15 sites, along with extended enrollment prior to account for this increase • Applicable updates made to study Inclusion and Exclusion Criteria including Synopsis and Section 8.4 to align with APOLLO Pivotal Trial criteria v10 • Clarification added for Heart Team specifications, study design language, and Investigational sites and Investigators section for	Additional recommendations post-procedurally align with preliminary findings from initial subject data available.	clearly define critical parameters of analysis for this study. Change in SAE reporting timeframe to align with program-wide standard for reporting timelines, may impact sponsor awareness of events.		

	increased specificity in definitions • Language added to distinguish point of enrollment within the study • Updated required labs at all study intervals • Removed urinalysis requirement at all study intervals • Clarified when TEE will be done in addition to TTE at follow-up intervals • Clarified quality of life questionnaires required at all follow-up intervals • Included Heart Failure Management and Medications • Added procedural adverse event collection and atrial septal defect as recommended for closure, along with 4th position role clarification during procedure • Recommendations at Discharge added for deep vein thrombosis and atrial septal defect • Updated table of assessments and Schedule of Events table to align with protocol updates in respective study sections • Updated MVARC defined outcomes and individual subject success in additional exploratory endpoints • Added non-reportable medical occurrences associated with the index procedure • Updated number of days to report UADEs and SAEs from 2 to 3 working days				

	• Clarified additional exploratory endpoints are measured through 5 year follow-up • Added details for subject exit, withdrawal, or discontinuation • Alignment of potential risks section and latest IFU with additional clarification on Risk minimization • Clarified membership for clinical events committee and data monitoring committee				