Early Feasibility Study of the Neovasc Tiara™ Mitral Transcatheter Heart Valve with the Tiara™ Transapical Delivery System (TIARA-I)

CLINICAL PROTOCOL

(Clinical Investigation Plan)

Clinical Study Number: 047-CPT-001

Version E

Effective Date: 17 November 2015

Study Sponsor:

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This clinical investigation will be performed in compliance with the protocol, ISO 14155:2011, *Clinical Investigations of Medical Devices for Human Subjects – Good Clinical Practice*, the FDA Good Clinical Practices (including the Investigational Device Exemptions [IDE] regulation), and other applicable regulatory requirements. The Clinical Investigation Plan complies with EN ISO 14155:2011.

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Clinical Investigation Plan Approval:

Printed Name of Medical Director	Signature of Medical Director	Date
Shmuel Banai	S. Banai	20 Nov 2015
Vicki Bebeau		19 NOV 2015
Printed Name of Sponsor	Signature of Sponsor	Date

Site Principal Investigator:

I have read and understand the contents of the protocol. I agree to conduct this study according to the requirements of the study protocol and in accordance with Good Clinical Practice and applicable regulations. I agree to supervise all Co-Investigators at my site as well as the use of all devices and study materials at my institution and to ensure appropriate informed consent is obtained from all subjects prior to inclusion in this study.

Printed Name of Investigator	Signature of Investigator	Date

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1 SYNOPSIS

Title:	**Neovasc Tiara™ Mitral Valve Early Feasibility Study** Early Feasibility Study of the Neovasc Tiara™ Mitral Transcatheter Heart Valve with the Tiara™ Transapical Delivery System
Study Objective:	To evaluate the safety and initial performance of the Neovasc Tiara Mitral Transcatheter Heart Valve with the Tiara Transapical Delivery System. Data collected in this clinical study will include 6-month safety and performance of the device and delivery system as well as up to 5-year clinical outcomes.
Intended Use:	The Neovasc Tiara Mitral Heart Valve, a self-expanding transcatheter mitral valve, and the transapical Tiara Delivery System are intended for use in symptomatic subjects with severe mitral regurgitation (MR) who are at high risk (as defined in the protocol) for open mitral valve surgery and who are deemed anatomically eligible for Transcatheter Mitral Valve Replacement (TMVR).
Study Design:	This Early Feasibility study is an international, multicenter, single-arm, prospective, safety and performance clinical study.
Number of Subjects and Follow-up:	A maximum of 30 subjects will be implanted in the study at a maximum of 10 sites. A maximum of 15 subjects will be implanted in the United States. It is estimated that 100 subjects will be screened. All implanted study subjects will be assessed at the following intervals: Screening, Baseline, Procedure, Day 1, hospital discharge (or 10 days, whichever is earlier), 30 days, 90 days, 180 days, 1 year, and once annually thereafter for 5 years.
Estimated Timeline:	First subject in: November 2014 Last subject in: March 2016 Last subject out: March 2021
Population:	Subjects, 18 years of age or older, with severe symptomatic mitral regurgitation who are at high risk for open mitral valve surgery and who are deemed anatomically eligible for TMVR.
Selected Eligibility Criteria:	**Inclusion Criteria:** 1. Age 18 years or older. 2. NYHA Class III or IV heart failure. 3. Severe symptomatic mitral regurgitation (Stage D) by 2014 AHA/ACC Valvular Heart Disease Guidelines [4] classification ***(several valve hemodynamic criteria are required for assessment of MR severity, but <u>not all criteria</u> for each category will be present in each subject)***:

Note: Subjects may have either primary (Degenerative) or secondary (Functional) MR. As per the guidelines, definition of Stage D varies by primary or secondary etiology.

	Primary (Degenerative)	Secondary (Functional)
Valve Anatomy	1. Severe mitral valve prolapse with loss of coaptation or flail leaflet 2. Rheumatic valve changes with leaflet restriction and loss of central coaptation 3. Prior Infective Endocarditis 4. Thickening of leaflets with radiation heart disease	1. Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet 2. Annular dilation with severe loss of central coaptation of the mitral leaflets
Valve Hemodynamics	1. Central jet MR >40% LA or holosystolic eccentric jet MR 2. Vena contracta ≥0.7 cm 3. Regurgitant volume ≥60 mL 4. Regurgitant fraction ≥50% 5. ERO ≥0.40 cm^2 6. Angiographic grade 3–4+	1. ERO ≥0.20 cm^2 2. Regurgitant volume ≥30 mL 3. Regurgitant fraction ≥50%

	Primary (Degenerative)	Secondary (Functional)
Hemodynamic Consequences/ Associated Cardiac Findings	1. Moderate or severe LA enlargement 2. LV enlargement 3. Pulmonary hypertension present	1. Regional wall motion abnormalities with reduced LV systolic function 2. LV dilation and systolic dysfunction due to primary myocardial disease
Symptoms	1. Decreased exercise tolerance 2. Exertional dyspnea	1. HF symptoms due to MR persist even after revascularization and optimization of medical therapy 2. Decreased exercise tolerance 3. Exertional dyspnea

4. High surgical risk for open mitral valve surgery as determined by the examining cardiac surgeon and the local institutional Heart Valve Team based on a Society of Thoracic Surgeons (STS) mitral valve replacement Predicted Risk of Mortality (PROM) ≥ 8% and/or the Heart Valve Team assessing the risk of operative mortality ≥ 8% (modified from 2014 AHA/ACC Valvular Heart Disease Guidelines definition of High Risk).
5. Subject meets the anatomical eligibility criteria for available size(s) of the Tiara Mitral Valve. Anatomical eligibility (beyond annulus size) will be determined by the Central Screening Committee (CSC).
6. The subject has been informed of the nature of the investigational device, required study follow-up procedures and visits and agrees to participate, and has provided written informed consent.

Exclusion Criteria:

1. Deemed too frail by objective frailty assessments or with severe comorbidities such that the subject is unlikely to benefit from the procedure as determined by the CSC.
2. Subject is listed for cardiac transplantation.

	3. Previous cardiac procedures: • PCI within 30 days of enrollment • Drug Eluting Stent implantation within 3 months of enrollment • Bare Metal Stent implantation within 30 days of enrollment • Coronary artery bypass graft (CABG) within 30 days of enrollment • Any previous mitral valve replacement surgery • Previous TAVR within 30 days of enrollment • Previous mitral valve repair surgery within 30 days of enrollment 4. Evidence of any myocardial infarction (MI) within 30 days of enrollment. 5. All cardiac structures will be reviewed and eligibility determined by the CSC: • Degree of mitral stenosis, mitral annular calcification, and other valve anatomic pathology • Previously implanted medical devices that may interfere with the procedure • Ventricular dysfunction with ejection fraction ≤ 25% within 30 days of enrollment • Left ventricular outflow tract (LVOT) obstruction • Evidence of left atrial and/or left ventricular thrombus (within 3 months of enrollment), vegetation or cardiac mass • Apex not amenable to transapical access as deemed by the examining cardiac surgeon(s) • Right ventricular (RV) dilatation or degree of right-sided failure • Severe tricuspid regurgitation (TR) • Presence of an intracardiac shunt • Clinically significant untreated Coronary Artery Disease (CAD) 6. Cerebrovascular accident and/or TIA within 30 days of enrollment. 7. Subjects who are on chronic hemodialysis or who have a creatinine value > 3.0 mg/dL. 8. Pregnant or planning pregnancy within next 12 months. 9. Documented bleeding or coagulation disorders which limit anticoagulant therapy.

	10. Documented recent (within 3 months of enrollment) GI bleeding. 11. Active infections requiring antibiotic therapy. 12. Known hypersensitivity or contraindication to: • Aspirin, or heparin, or clopidogrel (Plavix) • Allergy to contrast media which cannot be managed medically • Nitinol or its components (e.g., nickel or titanium) 13. Subject is unable to undergo transesophageal echocardiography (TEE) during the implantation procedure. 14. Subject is currently participating in another investigational drug or device clinical trial that may interfere with the results of either trial. (Note: Patients enrolled in a clinical trial involving products that are now commercially available are eligible). 15. Subjects with a life expectancy of less than 12 months outside of mitral valve-related disease.
Data Collection Time Points:	• Screening • Baseline • Procedure • Day 1/Post-procedure • Day 10/Discharge • 30 days • 90 days • 180 days • Annually to 5 years
Primary Safety and Effectiveness Endpoint:	• Freedom from all-cause mortality and major adverse events defined as disabling stroke, myocardial infarction (peri-procedural or spontaneous), renal failure requiring dialysis, life-threatening bleeding, and cardiac surgical or transcatheter reintervention at 30 days from the implant procedure or hospital discharge, whichever is later.
Secondary Endpoints:	• Freedom from all-cause mortality and major adverse events defined as disabling stroke, myocardial infarction (peri-procedural or spontaneous), renal failure requiring dialysis, life-threatening bleeding, and cardiac surgical or transcatheter reintervention at 90 days, 180 days, one (1) year and annually to five (5) years from the implant procedure.

	• Individual components of the primary endpoint (major adverse events of all-cause mortality, disabling stroke, myocardial infarction [peri-procedural or spontaneous], renal failure requiring dialysis, life-threatening bleeding, and cardiac surgical or transcatheter reintervention) at 30 days from the implant procedure or hospital discharge (whichever is later), 90 days, 180 days, 1 year, and annually to 5 years from the implant procedure.
	• Individual 30 day rates of the following ***device/procedure-related*** major adverse events (MAEs):
	  • All mortality
	  • All stroke
	  • Residual MR > mild (1+)
	  • Life threatening bleeding
	  • Acute Kidney Injury Grade 3
	  • New pacemaker/Left Bundle Branch Block (LBBB)
	  • Coronary occlusion/myocardial infarction
	  • Urgent/emergent surgery or reintervention
	• Composite safety endpoint of the following at 30 days or hospital discharge, whichever is later:
	  • Freedom from all cause mortality and
	  • Freedom from major adverse events defined as disabling stroke, myocardial infarction, renal failure requiring dialysis, life threatening bleeding, and cardiac surgical or transcatheter reintervention.
	• Progression of heart failure (HF) (readmission for HF, need for HF device implantation, cardiac transplantation or listing for transplantation) at 1 year from the implant procedure.
	• Incidence of mitral valvular insufficiency of ≥ moderate at post-procedure, discharge, 30 days, 90 days, 180 days, 1 year, and annually to 5 years as compared to baseline.
	• Incidence of the composite and of individual components of major adverse events (all-cause mortality, disabling stroke, myocardial infarction [peri-procedural or spontaneous], renal failure requiring dialysis, life-threatening bleeding, and cardiac surgical or transcatheter reintervention) at 90 days, 180 days, 1 year, and annually to year 5 from the implant procedure.
	• Device migration defined as any movement of any valve

	structure(s) compared with the final implant location, resulting in hemodynamic or patho-anatomic consequences (e.g., mitral paravalvular leak or left ventricular outflow tract obstruction).
	• Device fracture (adjudicated as affecting valve performance or not affecting valve performance).
	• Device success defined as (measured at each assessment interval):
	  • Successful delivery and deployment of the device in the correct position and retrieval of the delivery catheter resulting in:
	  • Mitral regurgitation < moderate (2+),
	  • Effective valve orifice area ≥ 1.5 cm^2 as assessed by post-procedural echocardiogram,
	  • MV gradient <5 mmHg,
	  • no migration, fracture, or endocarditis,
	  • stroke free,
	  • no additional valve/access related interventional or surgical procedures.
	• Procedure success defined as device success without the occurrence of procedure/device related major adverse events (defined above) in-hospital or at 30 days, whichever is later.
	• Performance (as assessed at 30 days, 90 days, 180 days, and once annually for 5 years as compared to baseline):
	  • Clinical performance as measured by NYHA Functional Class, 6 Minute Walk Test (6MWT), and the Kansas City Cardiomyopathy Questionnaire (KCCQ).
	  • Hemodynamic performance as assessed by echocardiography: mean MV gradient, mitral regurgitation, effective orifice area of the MV, LV systolic and diastolic dimensions as well as volume.
	  • Stroke free survival.
	  • Original intended device in place.
	  • No additional valve/access-related interventional or surgical procedures.
	• One (1) year non-hierarchical composite of device success and no need for HF hospitalization or HF hospitalization equivalent.

	• Individual patient success (6 months and 1 year) defined as device success and all of the following:
	  • No rehospitalizations or reinterventions for HF (includes HF hospitalization equivalents, new listing for heart transplant, need for VAD or CRT)
	  • NYHA class improvement by at least 1 level from baseline
	  • KCCQ improvement >10 vs. baseline
	  • 6MWT improvement >50 meters vs. baseline
	• Days alive and out of hospital at one (1) year.

Health Care Resource Utilization:	For subjects enrolled in the US, inpatient health care resource utilization will be assessed by collection of all hospital bills, charges submitted by hospitals to third party payers, and reimbursement to the hospitals.

2 INTRODUCTION

2.1 BACKGROUND

2.1.1 DISEASE PROCESS

Mitral regurgitation (MR) is the most prevalent significant valvular disease and affects up to 2% of the population, with an increasing incidence with age [1]. The prevalence of significant MR is 0.2% between the ages of 18–44 but rises to 10% in those ≥ 70 years old. With the aging of the population valvular heart disease and particularly MR is expected to rise even further. Indeed MR is > 2x more prevalent in the elderly than aortic valve disease, including aortic stenosis [2, 3].

MR may be either primary (also termed degenerative) or secondary (also termed functional) [4]. Primary mitral regurgitation in the developed world is most often due to mitral valve prolapse, which in the younger population presents with myxomatous degeneration of the valve while in older patients fibroelastic deficiency disease leads to chordal rupture. Secondary or functional MR may be caused by ischemic heart disease (usually with a previous myocardial infarction) or a cardiomyopathy. There are estimated to be between 1.6 and 2.8 million patients with secondary MR in the United States.

The presence of even moderate MR after a myocardial infarction is associated with a doubling of mortality [5]. As MR progresses patients develop worsening heart failure with LV dilatation, which further worsens the MR. Once significant LV dilatation and impaired LV function have occurred the prognosis following surgery is markedly worse. The

outcome in octagenerians is also poor. More than 50% of patients with severe MR who are potential candidates for surgery are denied this opportunity, most often due to comorbid conditions, advanced age, or impaired LV function [6].

2.1.2 ALTERNATIVE THERAPIES/TECHNIQUES

Surgical treatment, whether by mitral valve replacement (with either a mechanical valve or a bioprosthetic valve) or mitral valve repair, has been the standard therapeutic approach for severe mitral regurgitation. Additional surgical therapies include mitral annuloplasty and implantation of a Carpentier ring.

While surgical technique has improved many patients remain at high risk for surgery, defined by the AHA/ACC Guidelines as having an STS score of 8% or higher, or having significant frailty, two comorbid organ system compromises, or specific procedure-related impediments [4]. Recently various percutaneous techniques have been developed [7]. Technical innovations to reduce MR include percutaneous edge-to-edge leaflet plication, leaflet coaptation, leaflet ablation, direct or indirect annuloplasty, percutaneous chordal remodeling, and LV remodeling. While most of these percutaneous developments are either still in animal testing or in feasibility tests, the MitraClip (Abbott Cardiovascular System) was approved by the FDA in the United States for the treatment of degenerative severe symptomatic mitral regurgitation in patients who have too high a risk for surgery [8].

Medical therapy for severe mitral regurgitation includes use of diuretics, angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB), and beta blockers. Medical therapy, while of benefit in reducing congestive symptoms, is still associated with high morbidity and mortality in severe mitral regurgitation.

2.1.3 STUDY PURPOSE

The objective of this early feasibility study is to evaluate the safety and initial performance of the Neovasc Tiara Mitral Transcatheter Heart Valve with the Tiara Transapical Delivery System.

Data collected in this clinical study will include 6 month safety and performance of the device and delivery system as well as up to five-year clinical outcomes.

2.2 STUDY DEVICE

The Tiara Mitral Transcatheter Heart Valve is designed to be used in combination with the Tiara Delivery System for transapical mitral valve implantation in patients with severe symptomatic mitral regurgitation (Stage D by the 2014 AHA/ACC Valvular Heart Disease Guidelines classification) who are deemed to be at high risk for conventional mitral valve replacement.

The following devices will be available for clinical investigational use under this study:

Product Name	Valve Size	Model No.
Neovasc Tiara™ Mitral Transcatheter Heart Valve	35mm	TAMV001
Neovasc Tiara™ Delivery System (32Fr)	35mm	TADSTA001
Neovasc Tiara™ Mitral Transcatheter Heart Valve	40mm	40TAMV01
Neovasc Tiara™ Delivery System (36Fr)	40mm	36TAMDS01

2.2.1 DEVICE DESCRIPTION – TIARA VALVE

The Tiara Mitral Valve System (TMVS) (Figures 1 and 2) is a catheter-based self-expanding mitral bioprosthesis that is implanted using a transapical approach.

The Tiara valve is comprised of a medical-grade Nitinol stent with an electropolished finish and gold markers. The valve's three leaflets are made of glutaraldehyde-treated bovine pericardial tissue; Neovasc maintains an EDQM TSE certificate for bovine pericardium (R1-CEP 2008-116) and the company's quality system is certified to ISO 13485 for the design, development, manufacture, and distribution of bioprosthetic heart valves and components derived from bovine pericardial tissue. The atrial and ventricular "skirts" are made of medical-grade polyester fabrics. Each valve is packaged with an embossed polytetrafluoroethylene serial tag for identification.

It is specifically designed to fit the complex anatomical structure of the mitral apparatus. The valve assembly is D-shaped to match the natural orifice of the mitral valve and to prevent impingement of the aorta or obstruction of the left ventricular outflow tract. The Tiara valve does not rely solely on radial force for securement. The atrial (inflow) portion engages the area of the left atrium surrounding the mitral annulus. It has a full atrial skirt to reduce paravalvular leakage (PVL). The ventricular side is seated securely on the fibrous trigones and the posterior shelf (an area situated on the roof of the left ventricle behind the posterior mitral leaflet due to left ventricular dilation in MR patients). Anterior and posterior tabs engage the mitral leaflets and chordae within the left ventricle (outflow) to draw the native anatomy against the body of the valve to prevent PVL.

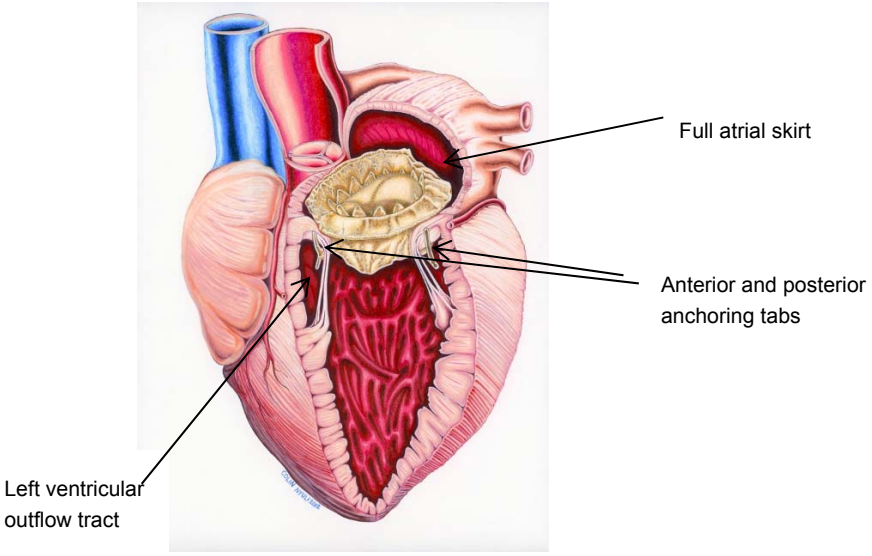

Figure 1: Tiara Valve in the Mitral Apparatus

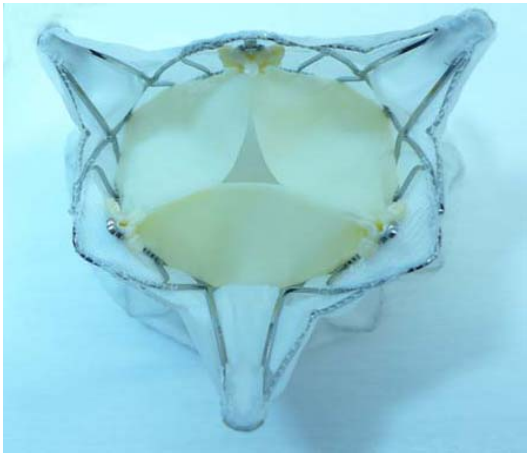

Figure 2: Tiara Valve

2.2.2 DELIVERY SYSTEM DESCRIPTION – TIARA DELIVERY SYSTEM

The 35mm Tiara valve is loaded onto a short 32Fr delivery catheter. The 32Fr Tiara delivery system (Figure 3) is utilized for loading of the 35mm valve and is compatible with a 0.035” guidewire.

The 40mm Tiara valve is loaded onto a short 36Fr delivery catheter. The 36Fr Tiara delivery system (Figure 4) is utilized for loading of the 40mm valve and is compatible with a 0.035” guidewire.

The distal (deployment) end of both the 32Fr and 36Fr systems feature an atraumatic, self-dilating tip. In addition, there is a radiopaque marker band embedded in the tip of the catheter, as well as a marker band embedded in the dilator tip. A protective sheath

covers and maintains the valve in the loaded configuration during placement. A central knob in the handle is used to advance and deploy the valve.

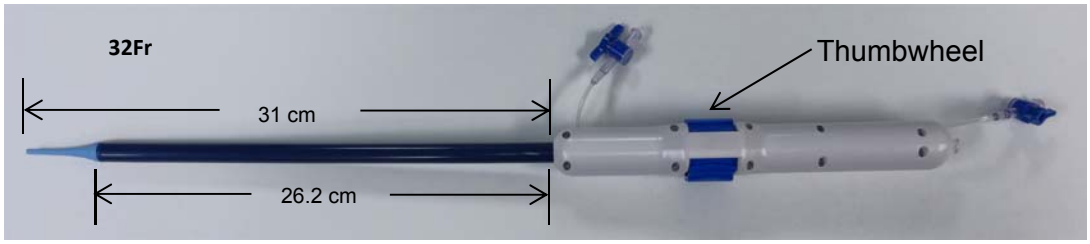

Figure 3: Tiara Delivery System – 32Fr

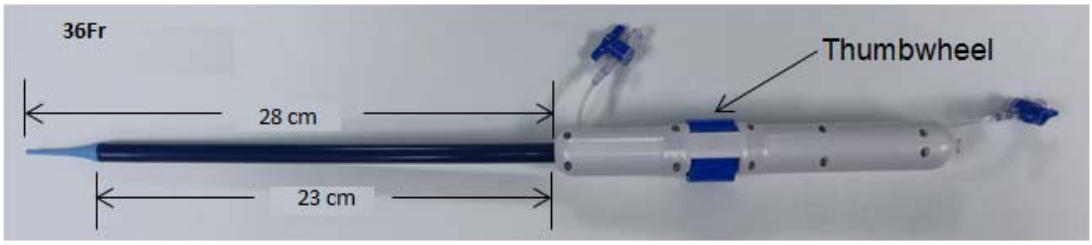

Figure 4: Tiara Delivery System – 36Fr

2.2.3 TIARA IMPLANT PROCEDURE

Tiara valve implantation is achieved transapically using a delivery system inserted through the apex of the heart. Deployment of the device is controlled by a single thumbwheel on the handle of the Tiara Delivery System and is guided by a combination of fluoroscopic and echocardiographic imaging (TEE). The patient is expected to remain hemodynamically stable throughout the procedure. Rapid pacing may be used for a short period (~10 seconds) during the final stage of the implant procedure to facilitate optimal placement of the prosthetic valve.

In all stages of valve deployment until the final step of deploying the ventricular tabs, it is possible to recapture the partially deployed valve into the delivery catheter, reposition and complete the implant procedure, or alternatively, at the discretion of the operator, withdraw the catheter and unimplanted valve from the patient.

Characteristics unique to the Tiara implant procedure (TMVR) vs. traditional mitral valve replacement (MVR) include:

- A mini-thoracotomy is utilized for transapical heart access with the Tiara implant vs. a full sternotomy with MVR
- There is no need for cardiopulmonary bypass with the Tiara implant
- Less anesthesia time is anticipated with the Tiara implant

- Quicker recovery time is anticipated with the Tiara implant
- Ability to treat subjects with the Tiara implant who are high risk for open heart surgery

2.2.4 PRIOR TESTING

The Tiara Mitral Valve System has been in development since 2009. Extensive preclinical testing has been conducted, as summarized below.

Nonclinical in vitro testing has been conducted in accordance with ISO 5840-3, *Cardiovascular implants – Cardiac valve prostheses – Part 3: Heart valve substitutes implanted by transcatheter techniques* and FDA's *Draft Guidance for Industry and FDA Staff – Heart Valves – Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications*. Tests include tensile strength, resheathing force, function testing, hydrodynamic performance, accelerated wear, corrosion resistance, magnetic resonance imaging (MRI) compatibility, radiopacity, and finite element analysis.

All biocompatibility testing was performed in accordance with Good Laboratory Practices (GLP) at an ISO 17025:2005 certified facility (NAMSA, Northwood OH). The valve and delivery system have met the requirements for cytotoxicity, sensitization, irritation, and hemocompatibility.

The magnetic resonance (MR) compatibility of the Nitinol (NiTi) stent of the Tiara Mitral Transcatheter Heart Valve was determined to be MRI conditional.

Animal studies were conducted to demonstrate the feasibility of various device design and procedure iterations.

Long-term testing in sheep has demonstrated that the device is well tolerated. Histology data showed an appropriate healing response to the implant, with mature collagenized fibrous tissue growth covering the stent frame. The myocardium adjacent to and beneath the anchoring structures showed scarring around the device without necrosis or significant inflammation.

2.2.5 PRIOR CLINICAL STUDIES

As of October 2015, Tiara valves have been implanted in nine (9) patients in Canada (St. Paul's Hospital, Vancouver, BC) through Health Canada's Special Access Programme.

This recent clinical experience demonstrates the importance of patient selection with the use of any transcatheter valve, which includes critical assessment of patient anatomy utilizing CT scan, TEE, and transthoracic echocardiography (TTE) prior to implantation to ensure appropriate sizing and positioning for device deployment.

The current protocol is calibrated to enroll such patients and in addition has a screening committee to ensure appropriate patient selection (Section 15.4).

3 RISK ANALYSIS

3.1 RISKS

3.1.1 RISKS ASSOCIATED WITH INVESTIGATIONAL PRODUCTS

There may be possible risks associated with the use of the TMVS including the Tiara Mitral Valve and the Tiara Delivery System; these risks include, but are not limited to:

- Access site complications (pain, bleeding, hematoma, pseudoaneurysm, infection)
- Accessory device failure
- Acute kidney injury (AKI)
- All-cause mortality
- Allergic reaction (e.g., to medications, contrast media, Nitinol)
- Anaphylactic shock/toxic reaction
- Aneurysm or pseudoaneurysm
- Angina
- Aortic valve damage or dysfunction
- Atrial perforation
- Bleeding, including anticoagulant/antiplatelet-related
- Cardiac arrhythmias/conduction disturbances
- Cardiac arrest
- Cardiac perforation
- Cardiogenic shock
- Cardiac failure/low cardiac output/decompensation/hemodynamic compromise
- Coronary flow obstruction due to compression of a coronary artery by the implanted Tiara valve
- Damage to the prosthetic valve
- Device embolization
- Device migration or malposition (requiring intervention)
- Device fracture
- Dyspnea
- Edema
- Embolization of debris – device- or procedure-related
- Endocarditis
- Esophageal irritation or perforation

- Failure to retrieve system components
- Hemolysis
- Hemolytic anemia
- Inability to complete implant procedure
- Increased procedure time
- Leak, transvalvular and/or paravalvular
- LVOT obstruction
- Mitral valve apparatus damage or dysfunction
- MRI incompatibility
- Myocardial infarction
- Myocardial perforation/rupture
- Neurological dysfunction (e. g., stroke, TIA, neurological changes/deficits)
- Nonstructural dysfunction (entrapment by pannus overgrowth/endothelialization)
- Structural deterioration, including but not limited to: calcification, leaflet tears, and/or chordal rupture(s)
- Systemic embolization
- Thrombosis, thromboembolism
- Transvalvular flow disturbances
- Valve deployment in unintended location
- Valve regurgitation
- Valve stenosis
- Valve thrombosis
- Virus or other transmissible agent

These adverse events/complications could lead to:

- Reoperation (non-emergent or emergent coronary bypass, heart valve replacement)
- Attempted recovery/explant
- Permanent disability
- Death
- Conversion to open surgery
- Transfusion
- Explantation
- Extended hospitalization
- Permanent pacemaker
- Multi-system organ failure

There are no known interactions of the study device(s) with concomitant medication.

3.1.2 RISKS ASSOCIATED WITH STUDY PROCEDURE

Complications associated with standard cardiac catheterization, the use of anesthesia, and the use of transcatheter heart valves via a transapical approach may include but are not limited to the following:

- Acute ventricular failure/rupture
- Abnormal lab values
- Allergic reaction to anesthesia or to contrast media
- Allergic reaction to antiplatelet agents and/or warfarin
- Anaphylactic shock/toxic reaction
- Anemia
- Angina
- Annulus rupture
- Arrhythmia
- Bleeding, procedure related; may require transfusion, medical, or surgical intervention
- Cardiovascular injury including perforation or dissection of vessels, atrium, ventricle, myocardium or valvular structures that may require intervention
- Conduction disturbances/system injury which may require a permanent pacemaker
- Coronary sinus perforation
- Dyspnea
- Embolization including air, thrombus, device particulates, calcific, external particulates
- Apical AV fistula or pseudoaneurysm
- Fever
- Heart failure
- Heart murmur
- Hematoma
- Hepatic dysfunction
- Hypertension/hypotension
- Infection including septicemia and endocarditis
- Inflammation/immunological reaction
- Myocardial infarction
- Neurological dysfunction (e.g., stroke, TIA, neurological changes/deficits)
- Pain or bruising at the access site
- Pericardial effusion/cardiac tamponade
- Pleural effusion

- Pulmonary edema
- Radiation injury
- Renal failure/insufficiency or acute kidney injury
- Respiratory insufficiency or respiratory failure
- Right heart failure
- Syncope
- Valve thrombosis
- Valve calcification

These adverse events/complications could lead to:

- Death
- Reoperation (non-emergent or emergent coronary bypass, heart valve replacement)
- Attempted recovery/explant
- Permanent disability
- Conversion to open surgery
- Transfusion
- Explantation
- Extended hospitalization
- Permanent pacemaker

3.1.3 RISK MANAGEMENT

Additional warnings and actions to minimize risks to the patient include (but are not limited to) the following:

- The devices are designed, intended, and distributed for single use only. Do not resterilize or reuse the devices. There is no data to support the sterility, nonpyrogenicity, and functionality of the devices after reprocessing.
- Correct sizing of the Tiara Mitral Transcatheter Heart Valve and native mitral annulus structure is essential to help prevent paravalvular leak, migration, and/or annular injury.
- Accelerated deterioration of the Tiara Mitral Transcatheter Heart Valve may occur in patients with an altered calcium metabolism.
- If pacing is used: Observation of the pacing lead throughout the procedure is essential to avoid the potential risk of pacing lead perforation.
- In the event of catastrophic failure of the device intra-procedure or post-procedure, the subjects might undergo open heart surgery.

- Clinical site qualifications will be conducted to ensure that Investigators with transapical experience, Heart Teams, and appropriate clinical research staff are available to support the study.
- Investigators will be required to undergo valve placement training in the animal or benchtop model prior to their first implant.
- A Central Screening Committee will evaluate each patient to determine eligibility which includes anatomical review based on core lab CT findings.
- An independent Data Safety Monitoring Board (DSMB)/Clinical Events Committee (CEC) will assess the trial in real time.

Additional details on product handling and procedure guidance should be followed per the Instructions For Use (IFU) and Investigator's Brochure (IB).

The Sponsor and the Executive Steering Committee (ESC) will help to assess and determine site and Investigator eligibility and ability to participate in the study by reviewing study progress and CIP compliance on an ongoing basis.

3.2 BENEFITS

The Tiara Mitral Transcatheter Heart Valve is designed to be used in combination with the Tiara Delivery System for transapical mitral valve implantation in patients with severe mitral regurgitation (both primary and secondary) requiring mitral valve replacement, who are deemed to be at high risk for conventional MVR. There are no guaranteed benefits from participation in this study. The potential benefits resulting from this study fall into the following categories:

- Direct benefit subject(s) may receive from participation in the study,
- Possible benefit subject(s) may receive from participation in the study,
- Possible benefit for future patient(s) receiving the Tiara Mitral Valve based upon results of the study.

Mitral valve replacement with the Neovasc Tiara Mitral Heart Valve with the transapical Tiara Delivery System may result in one or more of the following benefits:

- improved valvular function, alleviation of symptoms related to mitral regurgitation,
- improved quality of life and/or improved morbidity and mortality in patients with symptomatic severe MR that are high-risk for mitral valve surgery.

Specific potential benefits of the transapical approach include technically easier implantation than with a transseptal approach and reduced risk of vascular complications.

The long-term results of using the investigational Tiara Mitral Transcatheter Heart Valve are not known at the present time. Alternative treatments include palliative medical therapy, high-risk surgical replacement of the mitral valve, and mitral valve plication with the MitraClip (Abbott Vascular).

3.3 STUDY JUSTIFICATION

Symptomatic severe mitral regurgitation is associated with high morbidity and mortality with impaired quality of life. Surgical mitral valve repair or replacement is the treatment of choice. Many patients, due either to comorbidities or to reduced ejection fraction, are at high risk for a surgical approach and are therefore not suitable surgical candidates. The development of a transcatheter approach which can be accomplished on the beating heart without cardiopulmonary bypass may offer an important advance, with the possibility of reduction in both mortality and morbidity. The risks of the mitral implantation with the novel Tiara valve are therefore justified given the potential benefit of this scientific advance.

4 STUDY OBJECTIVES

4.1 PRIMARY OBJECTIVE

The objective of this feasibility study is to evaluate the safety and initial performance of the Neovasc Tiara Mitral Transcatheter Heart Valve with the Tiara Delivery System.

Data collected in this clinical study will include short-term safety and performance of the device and delivery system as well as up to five-year clinical outcomes.

4.1.1 PRIMARY ENDPOINT

- Freedom from all-cause mortality and major adverse events defined as disabling stroke, myocardial infarction (peri-procedural or spontaneous), renal failure requiring dialysis, life-threatening bleeding, and cardiac surgical or transcatheter reintervention at 30 days from the implant procedure or hospital discharge, whichever is later.

4.1.2 SECONDARY ENDPOINTS

- Freedom from all-cause mortality and major adverse events defined as disabling stroke, myocardial infarction (peri-procedural or spontaneous), renal failure requiring dialysis, life-threatening bleeding, and cardiac surgical or transcatheter

reintervention at 90 days, 180 days, one (1) year and annually to five (5) years from the implant procedure.

- Individual components of the primary endpoint (major adverse events of all-cause mortality, disabling stroke, myocardial infarction [peri-procedural or spontaneous], renal failure requiring dialysis, life-threatening bleeding, and cardiac surgical or transcatheter reintervention at 30 days from the implant procedure or hospital discharge (whichever is later), 90 days, 180 days, one (1) year and annually to five (5) years from the implant procedure.
- Individual 30 day rates of the following ***device/procedure-related*** major adverse events (MAEs):
    a) All mortality
    b) All stroke
    c) Residual MR > mild (1+)
    d) Life threatening bleeding
    e) Acute kidney injury Grade 3
    f) New pacemaker/LBBB
    g) Coronary occlusion/myocardial infarction
    h) Urgent/emergent surgery or reintervention
- Composite safety endpoint of the following at 30 days or hospital discharge, whichever is later:
    a) Freedom from all-cause mortality
    b) Freedom from MAEs defined as disabling stroke, myocardial infarction, renal failure requiring dialysis, life threatening bleeding, and cardiac surgical or transcatheter reintervention
- Progression of heart failure (HF) (readmission for HF, need for HF device implantation, cardiac transplantation or listing for transplantation) at 1 year from the implant procedure.
- Incidence of mitral valvular insufficiency of $\geq$ moderate at post-procedure, discharge, 30 days, 90 days, 180 days, 1 year, and annually to 5 years as compared to baseline.
- Incidence of the composite and of individual components of major adverse events (all-cause mortality, disabling stroke, myocardial infarction [peri-procedural or spontaneous], renal failure requiring dialysis, life-threatening bleeding, and cardiac surgical or transcatheter reintervention) at 90 days, 180 days, 1 year, and annually to year 5 from the implant procedure.
- Device migration defined as any movement of any valve structure(s) compared

with the final implant location, resulting in hemodynamic or patho-anatomic consequences (e.g., mitral paravalvular leak or left ventricular outflow tract obstruction).

- Device fracture (adjudicated as affecting valve performance or not affecting valve performance).
- Device success defined as (measured at each assessment interval):
    a) Successful delivery and deployment of the device in the correct position and retrieval of the delivery catheter resulting in:
        - Mitral regurgitation < moderate (2+),
        - Effective valve orifice area ≥ 1.5 cm^2 as assessed by post-procedural echocardiogram,
        - MV gradient < 5 mmHg,
        - no migration, fracture, or endocarditis,
        - stroke free,
        - no additional valve/access related interventional or surgical procedures.
- Procedure success defined as device success without the occurrence of procedure/device related major adverse events (defined above) in-hospital or at 30 days, whichever is later.
- Performance (as assessed at 30 days, 90 days, 180 days, and once annually for 5 years as compared to baseline):
    - Clinical performance as measured by NYHA Functional Class, 6MWT, and the KCCQ.
    - Hemodynamic performance as assessed by echocardiography: mean MV gradient, mitral regurgitation, effective orifice area of the MV, LV systolic and diastolic dimensions as well as volume.
    - Stroke free survival.
    - Original intended device in place.
    - No additional valve/access-related interventional or surgical procedures.
- One year non-hierarchical composite of device success and no need for HF hospitalization or HF hospitalization equivalent.
- Individual patient success (6 months and 1 year) defined as device success and all of the following:
    a) No re-hospitalizations or reinterventions for HF (includes HF hospitalization equivalents, new listing for heart transplant, need for VAD or CRT)

b) NYHA class improvement by at least 1 level from baseline
c) KCCQ improvement >10 vs. baseline
d) 6MWT improvement >50 meters vs. baseline

- Days alive and out of hospital at one (1) year.

5 STUDY DESIGN

This Early Feasibility study is an international, multicenter, single arm, prospective, study to evaluate the safety and performance of the Neovasc Tiara Mitral Valve System in subjects with symptomatic severe mitral regurgitation requiring mitral valve replacement who are at high risk for open chest surgery.

A maximum of 30 subjects, 18 years of age or older, will be implanted in this study at a maximium of 10 sites. A maximum of 15 subjects will be implanted in the United States. The other geographies included in this study include Canada and Western Europe. It is estimated that 100 subjects will be screened.

Subjects satisfying the inclusion criteria and exclusion criteria will be eligible to receive the Neovasc Tiara Mitral Transcatheter Heart Valve with the Tiara Delivery System via a TMVR procedure.

6 STUDY POPULATION

6.1 DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

The study population consists of subjects, greater than 18 years of age, with severe symptomatic mitral regurgitation (both primary and secondary) requiring mitral valve replacement who are at high risk for open chest surgery and who are deemed anatomically eligible for TMVR.

6.2 INCLUSION CRITERIA

The Principal Investigator has the responsibility of screening potential subjects to determine if the subject meets ***all*** of the following inclusion criteria:

1. Age 18 years or older.
2. NYHA Class III or IV heart failure.
3. Severe symptomatic mitral regurgitation (Stage D) by 2014 AHA/ACC Valvular Heart Disease Guidelines [4] classification (***several valve hemodynamic criteria are required for assessment of MR severity, but <u>not all criteria</u> for each category will be present in each subject***).

Note: Subjects may have either primary (Degenerative) or secondary (Functional) MR. As per the guidelines, definition of Stage D varies by primary or secondary etiology.

Stage D Symptomatic Severe Mitral Regurgitation is defined as:

	Primary (Degenerative)	Secondary (Functional)
Valve Anatomy	1. Severe mitral valve prolapse with loss of coaptation or flail leaflet 2. Rheumatic valve changes with leaflet restriction and loss of central coaptation 3. Prior Infective Endocarditis 4. Thickening of leaflets with radiation heart disease	1. Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet 2. Annular dilation with severe loss of central coaptation of the mitral leaflets
Valve Hemodynamics	1. Central jet MR > 40% LA or holosystolic eccentric jet MR 2. Vena contracta ≥ 0.7 cm 3. Regurgitant volume ≥ 60 mL 4. Regurgitant fraction ≥ 50% 5. ERO ≥ 0.40 cm^2 6. Angiographic grade 3–4+	1. ERO ≥ 0.20 cm^2 2. Regurgitant volume ≥ 30 mL 3. Regurgitant fraction ≥ 50%

	Primary (Degenerative)	Secondary (Functional)
Hemodynamic Consequences/Associated Cardiac Findings	1. Moderate or severe LA enlargement 2. LV enlargement 3. Pulmonary hypertension present	1. Regional wall motion abnormalities with reduced LV systolic function 2. LV dilation and systolic dysfunction due to primary myocardial disease
Symptoms	1. Decreased exercise tolerance 2. Exertional dyspnea	1. HF symptoms due to MR persist even after revascularization and optimization of medical therapy 2. Decreased exercise tolerance 3. Exertional dyspnea

4. High surgical risk for open mitral valve surgery as determined by the examining cardiac surgeon and the local institutional Heart Valve Team based on an STS mitral valve replacement PROM ≥ 8% and/or the Heart Valve Team assessing the risk of operative mortality ≥ 8% (modified from 2014 AHA/ACC Valvular Heart Disease Guidelines definition of High Risk [4]).
5. Subject meets the anatomical eligibility criteria for available size(s) of the Tiara Mitral Valve. Anatomical eligibility (beyond annulus size) will be determined by the Central Screening Committee (CSC).
6. The subject has been informed of the nature of the investigational device, required study follow-up procedures and visits, agrees to participate, and has provided written informed consent.

6.3 EXCLUSION CRITERIA

Patients must be excluded if ***any*** of the following exclusion criteria is present.

1. Deemed too frail by objective frailty assessments or with severe comorbidities such that the subject is unlikely to benefit from the procedure as determined by the CSC.

2. Subject is listed for cardiac transplantation.
3. Previous cardiac procedures:
    - PCI within 30 days of enrollment
    - Drug Eluting Stent implantation within 3 months of enrollment
    - Bare Metal Stent implantation within 30 days of enrollment
    - Coronary artery bypass graft (CABG) within 30 days of enrollment
    - Any previous mitral valve replacement surgery
    - Previous TAVR within 30 days of enrollment
    - Previous mitral valve repair surgery within 30 days of enrollment
4. Evidence of any myocardial infarction (MI) within 30 days of enrollment.
5. All cardiac structures will be reviewed and eligibility determined by the CSC:
    - Degree of mitral stenosis, mitral annular calcification, and other valve anatomic pathology
    - Previously implanted medical devices that may interfere with the procedure
    - Ventricular dysfunction with ejection fraction ≤ 25% within 30 days of enrollment
    - Left ventricular outflow tract (LVOT) obstruction
    - Evidence of left atrial and/or left ventricular thrombus (within 3 months of enrollment), vegetation or cardiac mass
    - Apex not amenable to transapical access as deemed by the examining cardiac surgeon(s)
    - Right ventricular (RV) dilatation or degree of right-sided heart failure
    - Severe tricuspid regurgitation (TR)
    - Presence of an intracardiac shunt
    - Clinically significant untreated Coronary Artery Disease (CAD)
6. Cerebrovascular accident and/or TIA within 30 days of enrollment.
7. Subjects who are on chronic hemodialysis or who have a creatinine value of > 3.0 mg/dL.
8. Pregnant or planning pregnancy within next 12 months.
9. Documented bleeding or coagulation disorders which limits anticoagulant therapy.
10. Documented recent (within 3 months of enrollment) GI bleeding.
11. Active infections requiring antibiotic therapy.

12. Known hypersensitivity or contraindication to:
    - Aspirin, or heparin, or clopidogrel (Plavix)
    - Allergy to contrast media, which cannot be managed medically
    - Nitinol or its components (e.g., nickel or titanium)
13. Subject is unable to undergo transesophageal echocardiography (TEE) during the implantation procedure.
14. Subject is currently participating in another investigational drug or device clinical trial that may interfere with the results of either trial. (Note: Patients enrolled in a clinical trial involving products that are now commercially available are eligible.)
15. Subjects with a life expectancy of less than 12 months outside of mitral valve-related disease.

6.4 EARLY WITHDRAWAL CRITERIA AND PROCEDURES

The Investigator will make every attempt to follow the subjects at each of the required assessment periods. If a subject withdraws (or is withdrawn) from the clinical study, the reason for the withdrawal will be documented in the subject's Case Report Form (CRF) and medical records. The Investigator should attempt to complete an unscheduled visit prior to the subject's exit.

Subjects will be withdrawn from the study for any of the following reasons:

- Subject Withdrawal

  The subject may withdraw voluntarily from the study at any time, at their request, without penalty or loss of benefits to which they are otherwise entitled.

- Physician Withdrawal

  The Principal Investigator also has the right to withdraw a subject if they feel it is in the best interest of the subject to do so.

- Lost to Follow-up

  If a subject cannot be reached for a follow-up visit, the Investigator will document the efforts made to contact the subject and/or efforts made to obtain medical records. If the subject cannot be reached, despite multiple modes of contacting the subject, or misses a visit, the subject will be considered "unable to contact" for that time interval. After three (3) documented unsuccessful attempts to contact the subject, a certified letter (or equivalent) will be sent to the subject's residence. If there is no response after the certified letter is sent, the subject will be considered "lost to follow-up" and exited from the study.

In all cases of study withdrawal, withdrawn subjects will not undergo further study follow-up procedures after the time of study exit. Reasons for withdrawal will be recorded on the appropriate CRF. A study subject that has been withdrawn from the study will not be replaced.

Death notifications/registries may also be utilized. In the event of a subject withdrawal or lost to follow-up, the Sponsor may opt to obtain the death certificate/record.

7 INVESTIGATIONAL DEVICE MANAGEMENT

7.1 DEVICE ACCOUNTABILITY AND RECORDS

All TMVS shipments will have an Investigational Product Packing List. Any hand-carried TMVS devices will be also be accompanied with an Investigational Product Packing List. The Principal Investigator or designee will receive the TMVS shipment and take inventory comparing it to the Investigational Product Packing List. The Investigational Product Packing List will be completed with the shipment receipt date, condition of the received devices and the signature of the study personnel. Both the Study Center and the Sponsor, Neovasc Medical Inc. (Neovasc) will maintain copies of all Investigational Device Records.

The Investigator will maintain a Device Accountability Log on all received, used and returned Neovasc TMVS devices/components for this study. The log will be kept with the study documents and will be available for review during Sponsor monitoring visits. Documentation on the log will include:

1. Tiara Mitral Valve serial number and size
2. Tiara Delivery System serial number and size
3. Subject study identification number
4. Date of use - if the device was not used, the date of return and a reason for the return will be provided

The Tiara Mitral Transcatheter Heart Valve and Transapical Delivery System inventory will be stored in a controlled, cool, dry and clean area. This area should be secured and only accessible to the Principal Investigator(s), and approved Study Personnel. Only Cardiovascular Surgeons and Interventional Cardiologists who have been trained on the use of the Neovasc TMVS devices and study protocol may implant TMVS investigational devices.

7.2 STUDY DEVICE RETURN

All unused (this includes any device that is opened but not used) Neovasc TMVS devices will be returned to Neovasc upon notice from the Sponsor. The Device Accountability Log must document any unused devices that have been returned. Neovasc will provide instructions and shipping materials for device return as applicable.

8 PROCEDURES AND METHODS

8.1 TRAINING OF INVESTIGATIONAL CENTER PERSONNEL

Study Investigator(s), Study Personnel, and study center clinical staff will be trained by Neovasc on the use of the Tiara Mitral Valve and Delivery System, the Clinical Protocol, and CRFs where applicable. Training will be documented on the “Training Record”, which all trainees must sign. Investigators will be required to undergo valve placement training in the animal or benchtop model prior to their first implant.

In addition, a Delegation of Authority Log will be completed at each investigational center designating which individuals are allowed to perform specific study-related tasks.

8.2 INFORMED CONSENT

Once the Investigator(s) have identified a patient that may be eligible for the study, the background of the proposed study and the benefits and risks of the study and procedures must be explained to the patient. Each patient shall be given ample time to read the entire Informed Consent Forms (ICFs) and ask questions in order to make an informed decision. The patient must sign the Institutional Review Board (IRB)/Ethics Committee (EC)/Research Ethics Board (REB) approved ICFs prior to any study procedures being performed. Failure to provide informed consent renders the patient ineligible for the study. The signed informed consents must be available for review by the Sponsor prior to the index procedure.

Two separate consents will be obtained for this study, a Screening Informed Consent and a Study Informed Consent. While the majority, and at times all, the necessary screening procedures will likely have been performed as part of standard of care for patients with severe symptomatic mitral regurgitation, all patients will be consented specifically for the screening process once they have been identified as potential candidates for this protocol. The Screening Informed Consent includes the potential patients consenting that data **(de-identified)** may be reviewed by the Central Screening Committee. It is noted that some, or even all, of the screening procedures may be part of standard of care in specific patients, and may therefore have been obtained prior to the signing of the screening consent.

The Study Informed Consent should be obtained only after approval of the subject by the Central Screening Committee for continuation in the trial. Upon signature of the Study Informed Consent, the subject will be eligible for the TMVR procedure and implantation.

8.3 SUBJECT ENROLLMENT

A patient will be considered enrolled into the study and assigned a subject enrollment number after the subject has signed and dated the Screening Informed Consent.

8.4 SUBJECT SCREENING (UP TO 3 MONTHS PRIOR TO PROCEDURE)

All symptomatic subjects diagnosed with severe symptomatic mitral regurgitation requiring mitral valve replacement seen by the Investigator(s) should be pre-screened for eligibility.

Prior to collection of screening data, all potentially eligible subjects must sign the Screening Informed Consent as described in Section 8.2 above.

Any subject deemed ineligible due to time-window related exclusion criteria may be re-screened at a later time. If a subject is re-screened at a later date, the subject must review and sign the Screening Informed Consent and all enrollment criteria must be established based on the most recent information available. Re-screened subjects will be issued a new Subject ID.

The screening procedures must be done no more than three months prior to the proposed procedure date, except as noted specifically.

The following information may be reviewed by the Central Screening Committee (the CSC may also request additional information):

1. History and physical including neurological exam, prior surgeries, and cardiac procedures
2. Medications (including review of guideline directed medical therapy [GDMT] for heart failure)
3. ECG*
4. STS Risk Score/EuroSCORE II
5. Canadian Study of Health and Aging (CSHA) 7-Point Clinical Frailty Scale
6. NIH Stroke Scale/Modified Rankin Scale
7. NYHA class
8. Chemistry profile[1], CBC with differential, PT/INR/PTT
9. Pregnancy test in women of childbearing potential

10. BNP or NTProBNP (whichever test is completed at screening should be collected throughout the duration of study)
11. Transthoracic echocardiogram (TTE)*
12. Transesophageal echocardiogram (TEE)*
13. Dynamic computed tomography (CT) of the chest with contrast (without contrast in those with eGFR < 40 ml/min)*
14. Coronary angiography (may be up to 6 months prior to the procedure)*
15. Adverse Events

*Source documents/images will be reviewed for these tests

[1] Na, K, Cl, BUN, Creatinine, Albumin, SGOT/AST, SGPT/ALT, Alkaline Phosphatase, Glucose, LDH

8.5 STUDY VISITS AND PROCEDURES

The following visits and study related procedures and tests will take place after the subject has been approved by the CSC and provides Study Informed Consent.

8.5.1 BASELINE VISIT (UP TO 7 DAYS PRIOR TO THE PROCEDURE)

Any testing conducted at the Screening visit within 7 days of the procedure may be utilized as Baseline data and does not have to be repeated for the Baseline visit.

1. Informed consent for TMVR with Tiara
2. Physical exam including neurological exam[1]
3. Pregnancy test in women of childbearing potential
4. Listing of current medications
5. NYHA class
6. Chemistry panel[2]
7. CBC with differential
8. Reticulocyte count
9. PT(INR)/PTT
10. Plasma free hemoglobin
11. Haptoglobin
12. NTProBNP or BNP
13. Troponin I or T

14. Optional plasma sample for banking (10 ml of blood)
15. QoL survey (KCCQ)
16. NIH Stroke Scale/Modified Rankin Scale
17. STS Risk Score/EuroSCORE II
18. Canadian Study of Health and Aging (CSHA) 7-Point Clinical Frailty Scale
19. 6 Minute Walk Test (6MWT)
20. ECG
21. Adverse Events

[1] If a stroke, TIA or change in neurological status has occurred, a neurological exam should be performed by a neurologist.

[2] Na, K, Cl, Glucose, BUN, Creatinine, Albumin, SGOT/AST, SGPT/ALT, Alkaline Phosphatase, LDH

8.5.2 PROCEDURE VISIT

Antibiotic prophylaxis will be given according to standard practice for valve implantation at each hospital.

Transapical access will be conducted per site standard of care to allow for delivery system insertion and valve deployment. The procedure will be done under TEE and fluoroscopic/angiographic guidance which will be recorded.

Neovasc personnel will be present during the procedure to load the valve into the delivery system, and a physician proctor will also be present to provide oversight to the implanting physician.

During the procedure all medications and the subject's vital signs will be monitored as per standard catheterization/operating room procedures. The ACT levels will be monitored and adjusted to keep > 250 seconds during the procedure (see section 10.1).

An angiogram to evaluate coronary patency must be completed after implantation of the Tiara Mitral Transcatheter Heart Valve prior to exit from the operating/hybrid procedure room.

All intraoperative AEs will be recorded.

1. Listing of medications administered
2. TEE
3. Cine/angiogram of the procedure
4. Radiation monitoring (fluoroscopy time and radiation exposure)

5. Adverse events

8.5.3 DAY 1 POST-PROCEDURE

1. Physical exam including neurological exam[1]
2. Chemistry panel[2]
3. CBC with differential
4. Reticulocyte count
5. PT(INR)/PTT
6. Troponin I or T
7. ECG
8. Adverse events

[1] If a stroke, TIA or change in neurological status has occurred, a neurological exam should be performed by a neurologist.

[2] Na, K, Cl, Glucose, BUN, Creatinine, Albumin, SGOT/AST, SGPT/ALT, Alkaline Phosphatase, LDH

8.5.4 DISCHARGE OR AT DAY 10 (WHICHEVER IS EARLIER)

1. Physical exam including neurological exam[1]
2. Current medications
3. NYHA class
4. Chemistry panel[2]
5. CBC with differential
6. PT/INR
7. Reticulocyte count
8. BNP or NTProBNP
9. ECG
10. NIH Stroke Scale/Modified Rankin Scale
11. TTE (may be performed up to 24 hrs prior to discharge if necessary for scheduling purposes)
12. Adverse events

[1] If a stroke, TIA or change in neurological status has occurred, a neurological exam should be performed by a neurologist.

[2] Na, K, Cl, Glucose, BUN, Creatinine, Albumin, SGOT/AST, SGPT/ALT, Alkaline Phosphatase, LDH

8.5.5 30 DAY VISIT (+ 7 DAYS)

1. Physical exam including neurological exam[1]
2. Current medications
3. NYHA class
4. Chemistry panel[2]
5. CBC with differential
6. PT/INR
7. Reticulocyte count
8. Plasma free hemoglobin
9. Haptoglobin
10. BNP or NTProBNP
11. Optional plasma sample for banking (10 ml of blood)
12. ECG
13. NIH Stroke Scale/Modified Rankin Scale
14. TTE
15. QoL survey (KCCQ)
16. 6MWT
17. Cine (of the valve)
18. Examination for radiation injury
19. Dynamic computed tomography (CT) of the chest with contrast (without contrast in those with creatinine clearance < 40 ml/min)*
20. Adverse Events

[1] If a stroke, TIA or change in neurological status has occurred, a neurological exam should be performed by a neurologist.

[2] Na, K, Cl, Glucose, BUN, Creatinine, Albumin, SGOT/AST, SGPT/ALT, Alkaline Phosphatase, LDH

8.5.6 90 DAY VISIT (± 14 DAYS)

1. Physical exam including neurological exam[1]
2. Current medications
3. NYHA class
4. Chemistry panel[2]
5. CBC with differential
6. Reticulocyte count
7. BNP or NTProBNP
8. Plasma free hemoglobin
9. Haptoglobin
10. Optional plasma sample for banking (10 ml of blood)
11. ECG
12. TTE
13. QoL survey (KCCQ)
14. 6MWT
15. NIH Stroke Scale/Modified Rankin Scale
16. Adverse events

[1] If a stroke, TIA or change in neurological status has occurred, a neurological exam should be performed by a neurologist.

[2] Na, K, Cl, Glucose, BUN, Creatinine, Albumin, SGOT/AST, SGPT/ALT, Alkaline Phosphatase, LDH

8.5.7 180 DAY VISIT (± 21 DAYS)

1. Physical exam including neurological exam[1]
2. Current medications
3. NYHA class
4. Chemistry panel[2]
5. CBC with differential
6. Reticulocyte count
7. Plasma free hemoglobin

8. Haptoglobin
9. BNP or NTProBNP
10. Optional plasma sample for banking (10 ml blood)
11. ECG
12. TTE
13. QoL survey (KCCQ)
14. 6MWT
15. NIH Stroke Scale/Modified Rankin Scale
16. Adverse events

[1] If a stroke, TIA or change in neurological status has occurred, a neurological exam should be performed by a neurologist.

[2] Na, K, Cl, Glucose, BUN, Creatinine, Albumin, SGOT/AST, SGPT/ALT, Alkaline Phosphatase, LDH

8.5.8 ANNUAL (YEARS 1–5) (± 30 DAYS)

1. Physical exam including neurological exam[1]
2. Current medications
3. NYHA class
4. Chemistry panel[2]
5. CBC with differential
6. Reticulocyte count
7. Plasma free hemoglobin
8. Haptoglobin
9. BNP or NTProBNP
10. Optional plasma sample for banking (10 ml of blood)
11. ECG
12. TTE
13. QoL survey (KCCQ)
14. 6MWT
15. NIH Stroke Scale/Modified Rankin Scale

16. Canadian Study of Health and Aging (CSHA) 7-Point Clinical Frailty Scale (at 1 Year visit only)
17. Endpoint-related adverse events (after Year 1 Visit)

[1] If a stroke, TIA or change in neurological status has occurred, a neurological exam should be performed by a neurologist.

[2]Na, K, Cl, Glucose, BUN, Creatinine, Albumin, SGOT/AST, SGPT/ALT, Alkaline Phosphatase, LDH

8.5.9 UNSCHEDULED VISITS

Subjects may also have unscheduled visits if significant medical issues or events occur, at the discretion of the Investigator. The following minimum data will be collected for unscheduled visits:

1. Updated history and physical including neurological exam[1]
2. Medication update
3. NYHA class
4. Adverse events

[1] If a stroke, TIA or change in neurological status has occurred, a neurological exam should be performed by a neurologist.

9 HEALTH CARE RESOURCE UTILIZATION

In order to obtain preliminary information regarding health care resource utilization, all US sites will be asked to collect hospital bills, third party insurance claims, and reimbursement information. All subjects will be consented to allow collection of this information and all such records will be deidentified in keeping with the Health Insurance Portability and Accountability Act (HIPAA) privacy regulations prior to being sent to the Sponsor or CRO.

10 MEDICATIONS AND FOLLOW-UP VISITS

10.1 ANTICOAGULATION/ANTIPLATELET THERAPY

All subjects should receive concomitant anticoagulation and antiplatelet therapy medications as outlined in Table 1.

Intra-procedurally, the activated clotting time (ACT) should be monitored, recorded and adjusted to keep the subject's ACT > 250 sec.

Post-procedure:

- Subjects in normal sinus rhythm: low-dose aspirin (100 mg or less daily) OR clopidogrel (75 mg daily) indefinitely AND warfarin or equivalent vitamin K antagonist for three months.
- Subjects in atrial fibrillation: low-dose aspirin (100 mg or less daily) OR clopidogrel (75 mg daily) AND warfarin or equivalent vitamin K antagonist indefinitely.

Subjects who are within a year post-DES implantation, have an ACS episode during the period of mandated warfarin therapy (three months), or have AF and require indefinite anticoagulation will receive warfarin plus either ASA + clopidogrel OR clopidogrel alone at the physician's discretion, based upon bleeding risk.

Note: Novel anticoagulants (e.g., dabigatran, apixaban, rivaroxaban, edoxaban, etc.) should not be used in lieu of warfarin during the three months of mandated warfarin treatment.

Note: Prasugrel and Ticagrelor should NOT be used in combination with anticoagulation (vitamin K antagonist) in this protocol.

Table 1: Concomitant Anticoagulation/Antiplatelet Medication Recommendations

Medication	Pre-Procedure	During Procedure	Post-Procedure	Initial 3 Months Post-Procedure	After Initial 3 Months Post-Procedure
Aspirin or Clopidogrel*	ASA: 75–100 mg if on chronic ASA; otherwise 300–325 mg loading -or- Clopidogrel: 75 mg for minimum 5 days or 600 mg loading	N/A	ASA: 75–100 mg QD -or- Clopidogrel:75 mg QD	ASA 75–100 mg QD for life -or- Clopidogrel: 75 mg QD	ASA: 75–100 mg QD for life -or- Clopidogrel: 75 mg QD

Medication	Pre-Procedure	During Procedure	Post-Procedure	Initial 3 Months Post-Procedure	After Initial 3 Months Post-Procedure
Warfarin	None	None	INR Goal: 2–3 for 3 mos if in NSR INR Goal: 2–3 indefinitely if in AF	INR Goal: 2–3 for 3 mos if in NSR INR Goal: 2–3 indefinitely if in AF	If in NSR: none INR Goal: 2–3 indefinitely if in AF

* Note: If the subject has an indication for dual antiplatelet therapy (DAPT) post-PCI or post-ACS and is also indicated as above for warfarin, aspirin and clopidogrel may be given in combination with warfarin (Triple Therapy) or either aspirin or clopidogrel may be held at the Investigator's discretion due to bleeding risk.

The following recommendations should be considered:

- Ensure no evidence of bleeding from the surgical site prior to starting any anticoagulation.
- Do **not** give a loading dose of Coumadin.
- Wait 24-48 hours post implant before starting Coumadin.

Closely monitor INRs while administering anticoagulation to achieve an INR Goal of 2-3. Continue to monitor INRs closely to ensure stability.

10.2 GUIDELINE DIRECTED MEDICAL THERAPY

Guideline directed medical therapy based on AHA/ACC or national guidelines should be given post-procedure with particular attention to heart failure and concomitant CAD and hyperlipidemia.

Subjects should receive antibiotic prophylaxis for endocarditis per the recommendations of the AHA or ESC (or national guidelines) for heart valve recipients.

10.3 SCHEDULING FOLLOW-UP VISITS/MISSED SUBJECT VISITS

At each follow-up assessment, the Investigator(s) or designee will need to determine the subject's availability for future follow-up. If any subject needs to be seen at a time other than a regularly scheduled follow-up visit, the same information as described above will be documented by the Investigator on the appropriate CRFs and indicated as an Unscheduled Visit. Follow-up information obtained by physicians outside of the investigational center will be documented and sent to the Investigator.

The Investigator(s) or designee will make every attempt to follow the subjects and will document the information gathered during the follow-up visits on the CRFs. Subjects will be encouraged by the Investigator(s) or designee to report any address or telephone number changes to the investigational center. The subject will also be informed of the importance of returning for scheduled follow-up visits even if they are not having any problems. The Investigator(s) will make every attempt to follow the subject.

The Investigator or designee should keep a separate log of the subjects' names and current addresses to facilitate their record keeping and ability to contact the subjects for future follow-up. If a subject cannot be reached for a follow-up assessment, the Investigator(s) will document it on the appropriate CRF for that interval as a 'missed visit' and will comment on the effort made to contact that subject, the subject's primary health care provider, and/or hospital records. Subjects who miss a visit will not be considered withdrawn, and an effort to recontact them will be made by the Investigator(s) or designee at the next follow-up interval.

10.4 CLINICAL STUDY TERMINATION

The Principal Investigator(s), the EC/IRB/REB and any applicable regulatory authorities will be notified in writing upon termination of the study. The Sponsor retains the right to suspend or terminate this clinical study at any time. The DSMB/CEC associated with the study may recommend termination should safety concerns warrant such action.

10.5 DATA COLLECTION METHODS

All required data for this study are to be collected with standardized CRFs for individual subjects. The CRFs must be signed by the Principal Investigator or Co-Investigator listed on the Clinical Trial Agreement (CTA) for each subject enrolled in the study. Study Coordinators or a designee at each clinical site will perform primary data collection drawn from source document reviews. Collection and recording of subject data should be kept current to reflect subject status during the course of the study. The CRFs will be completed prospectively and in a timely manner.

CRF Instructions will be provided to assist the Investigator(s) and Study Coordinators in the completion of the required CRFs.

Primary data collection on the CRFs will be based on source document reviews performed by Study Coordinators or a designee at each clinical site. All applicable CRFs will be available to the Study Coordinator as new patients are enrolled in the study.

All clinical sites will be monitored periodically by the Sponsor or its designee for protocol adherence, accuracy of CRFs, and compliance to applicable regulations. Evident patterns of non-compliance with respect to these standards will be cause for corrective

action. If corrective actions are not subsequently undertaken, the clinical site will be asked to withdraw from the trial.

10.6 SOURCE DOCUMENTATION REQUIREMENTS

Required study data are to be recorded in the subject's medical chart or on a study-specific source documentation form.

Regulations require that Investigators maintain information in the study subjects' medical records to verify data collected on the CRFs. In order to comply with these regulatory requirements, the following information will be verified as required by the Clinical Research Associate (CRA), and/or/designee and/or regulatory inspectors:

1. Medical history and physical condition of the study patient before involvement in the study sufficient to verify protocol entry criteria.
2. Dated and signed notes in the patient's medical record specifying the date of and names of person(s) conducting the informed consent discussions and date of consent signature.
3. Dated and signed notes from each study subject visit with reference to the CRFs for further information, if appropriate (for specific results of procedures and exams).
4. Notations on abnormal lab results and adverse events reported and their resolution.
5. Notes regarding concomitant medications taken during the study.
6. Study subject's condition upon completion of or withdrawal from the study.

10.7 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

Because of the potential for errors, inaccuracies, and illegibility in transcribing data, originals or photocopies of all relevant procedural records and reports, post-procedural examinations, laboratory and other test results may be kept on file.

11 DATA MANAGEMENT

Data management will be in charge of collecting and tracking data and instituting quality control measures for data entry verification and trial compliance. Data Management will query sites when entries in the CRFs are flagged for possible errors. Neovasc will review SAEs, SADEs, UADEs and significant protocol deviations from the clinical protocol, and ensure that such information is provided to Regulatory Authorities, Investigators, ECs, the DSMB and the ESC as required by regulations and this CIP.

12 REPORTABLE EVENTS/EFFECTS

12.1 REPORTING EXPECTATIONS

Adverse events will be recorded on the applicable CRFs (event, date of onset, severity, duration, relationship to device and procedure) by the Investigator or Research Coordinator, and will be followed until they are adequately resolved or explained.

Notification of adverse events to Neovasc may be completed via telephone, fax email, or through the electronic database (EDC). Reportable adverse events will be submitted to the applicable EC/IRB/REB and regulatory authorities per national and local reporting regulations and requirements.

All adverse events will be collected and reported to the Sponsor through the one year follow-up visit. After the one year follow-up visit and through the five year follow-up visit, only endpoint-related events will be collected and reported to the Sponsor. Any event that is deemed device-related shall be reported to the Sponsor regardless of the event severity.

12.2 ADVERSE EVENT

An adverse event is defined in ISO 14155:2011 as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

12.3 ADVERSE DEVICE EFFECT

An adverse device effect is defined in ISO 14155:2011 as an adverse event related to the use of an investigational medical device. This definition includes any event resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

12.4 SERIOUS ADVERSE EVENT

A serious adverse event (SAE) is defined in ISO 14155:2011 as an adverse event that: led to death; led to a serious deterioration in the health of the subject, that either resulted in a life-threatening illness or injury, or a permanent impairment of a body structure or a body function, or inpatient or prolonged hospitalization, or medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function; or led to fetal distress, fetal death or a congenital abnormality or birth defect. A planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered an SAE.

12.5 SERIOUS ADVERSE DEVICE EFFECT

A serious adverse device effect (SADE) is defined in ISO 14155:2011 as an adverse device effect that resulted in any of the consequences characteristic of a serious adverse event.

The Investigator(s) will report any serious device-related adverse event on the applicable CRFs and to the Sponsor no later than three days, followed by a written report in ten working days after the Investigator(s) first learns of the event.

It is preferable for the Investigator to notify the Sponsor within 24 hours of occurrence or knowledge of the device-related event.

12.6 UNANTICIPATED ADVERSE DEVICE EFFECT

Unanticipated adverse device effect (UADE) is defined in 21 CFR 812.3 as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the Investigational Plan, Clinical Investigator's Brochure (CIB), Clinical Protocol, or Instructions For Use (IFU), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

The Investigator(s) will report any unanticipated device-related adverse event to the Sponsor no later than three days, followed by a written report in ten working days after the Investigator(s) first learns of the event.

It is preferable for the Investigator to notify the Sponsor within 24 hours of occurrence or knowledge of the device related event.

12.7 DEATHS AND EXPLANTS

12.7.1 SUBJECT DEATHS

In the event of subject death, every effort should be made to obtain a copy of the autopsy report and/or death summary and/or death certificate. Information on the cause of death and its relationship to the study device will be determined by the Principal Investigator and recorded on the appropriate CRFs for study termination.

If a device is explanted during autopsy, the device should be returned to Neovasc for analysis. Return kits for devices will be provided upon request by the Principal Investigator or the Sponsor.

12.7.2 DEVICE EXPLANTS

In the event a device is explanted, every effort should be made to obtain a copy of the explant procedure report. Information on the cause of explant and its relationship to the study device will be determined by the Principal Investigator and recorded on the appropriate CRFs. Copies of an explant report, if available, should be included with the source documentation. The device should be returned to Neovasc or designee for analysis. Return kits for devices will be provided upon request by the Principal Investigator or the Sponsor.

12.8 DEVICE DEFICIENCY, FAILURE, MALFUNCTION, AND MISUSE

Device Deficiency, Failure, Malfunction, and Misuse information will be collected throughout the study. Device Failures (event, date of onset, severity, duration, and relationship) will be recorded on the applicable CRFs.

1. Device Deficiency: Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.
2. Device Failure: A device has failed if it is used in accordance with the Instructions For Use (IFU), but does not perform according to the IFU and negatively impacts the treatment.
3. Device Malfunction: A device malfunction is a failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the IFU or CIP.
4. Device Misuse: A misused device (one that is used by the Investigator in a manner that is contradictory to the IFU) will not be considered a malfunction.

13 STATISTICAL ANALYSIS

The main objective of this study is to demonstrate the safety of the Neovasc TMVR system, while gathering preliminary information on device performance and clinical outcomes. The trial is therefore designed to minimize the number of subjects exposed to the experimental device while still providing enough information for a preliminary indication of safety and performance before proceeding to larger clinical trials. A sample size of 30 subjects was chosen based on historical and regulatory experience with feasibility studies with transcatheter heart valves.

13.1 ANALYSIS POPULATIONS

Intent-to-Treat (ITT) Population: All subjects who have been enrolled in the study. A subject is considered enrolled in this population once they have met the

inclusion/exclusion criteria and have signed the Study Informed Consent and have had the procedure initiated (defined as skin incision).

NOTE: Subjects who have signed the Study Informed Consent but have not had the procedure initiated (defined as skin incision) will not be part of the ITT population but will be followed for 30 days for SAEs.

Treated Population: All subjects who have received the Tiara valve.

Per Protocol Population: All subjects who have received the Tiara valve and without major protocol deviations.

Screening Safety Population: All subjects who have consented to the screening and baseline visit process. SAEs occurring within 30 days of a screening procedure will be reported to the Sponsor.

13.1.1 PRIMARY ENDPOINT

- Freedom from all-cause mortality and major adverse events defined as disabling stroke, myocardial infarction (peri-procedural or spontaneous), renal failure, requiring dialysis, life-threatening bleeding, and cardiac surgical or transcatheter reintervention at 30 days from the implant procedure or hospital discharge, whichever is later.

13.1.2 SECONDARY ENDPOINTS

- Freedom from all-cause mortality and major adverse events defined as disabling stroke, myocardial infarction (peri-procedural or spontaneous), renal failure, requiring dialysis, life-threatening bleeding, and cardiac surgical or transcatheter reintervention at 90 days, 180 days, one (1) year and annually to five (5) years from the implant procedure.
- Individual components of the primary endpoint (major adverse events of all-cause mortality, disabling stroke, myocardial infarction [peri-procedural or spontaneous], renal failure requiring dialysis, life-threatening bleeding, and cardiac surgical or transcatheter reintervention) at 30 days from the implant procedure or hospital discharge (whichever is later), 90 days, 180 days, 1 year, and annually to 5 years from the implant procedure.
- Individual 30 day rates of the following ***device/procedure-related*** major adverse events (MAEs):
    - All mortality
    - All stroke
    - Residual MR > mild (1+)

- Life threatening bleeding
- Acute Kidney Injury Grade 3
- New pacemaker/LBBB
- Coronary occlusion/myocardial infarction
- Urgent/emergent surgery or re-intervention

- Composite safety endpoint of the following at 30 days or hospital discharge, whichever is later:
  - Freedom from all cause mortality and
  - Freedom from major adverse events defined as disabling stroke, myocardial infarction, renal failure requiring dialysis, life threatening bleeding, and cardiac surgical or transcatheter reintervention.
- Progression of heart failure (readmission for HF, need for HF device implantation, cardiac transplantation or listing for transplantation) at 1 year from the implant procedure.
- Incidence of mitral valvular insufficiency of ≥ moderate at post-procedure, discharge, 30 days, 90 days, 180 days, 1 year, and annually to 5 years as compared to baseline.
- Incidence of the composite and of individual components of major adverse events (all-cause mortality, disabling stroke, myocardial infarction [peri-procedural or spontaneous], renal failure requiring dialysis, life-threatening bleeding, and cardiac surgical or transcatheter reintervention) at 90 days, 180 days, 1 year, and annually to year 5 from the implant procedure.
- Device migration defined as any movement of any valve structure(s) compared with the final implant location, resulting in hemodynamic or patho-anatomic consequences (e.g., mitral paravalvular leak or left ventricular outflow tract obstruction).
- Device fracture (adjudicated as affecting valve performance or not affecting valve performance).
- Device success defined as (measured at each assessment interval):
  - Successful delivery and deployment of the device in the correct position and retrieval of the delivery catheter resulting in:
    - Mitral regurgitation < moderate (2+),
    - Effective valve orifice area ≥ 1.5 cm^2 as assessed by post-procedural echocardiogram,
    - MV gradient <5 mmHg,
    - no migration, fracture, or endocarditis,
    - stroke free,

    - no additional valve/access related interventional or surgical procedures.
- Procedure success defined as device success without the occurrence of procedure/device related major adverse events (defined above) in-hospital or at 30 days, whichever is later.
- Performance (as assessed at 30 days, 90 days, 180 days, and once annually for 5 years as compared to baseline):
    - Clinical performance as measured by NYHA Functional Class, 6MWT, and the KCCQ
    - Hemodynamic performance as assessed by echocardiography: mean MV gradient, mitral regurgitation, effective orifice area of the MV, LV systolic and diastolic dimensions as well as volume
    - Stroke free survival
    - Original intended device in place
    - No additional valve/access-related interventional or surgical procedures
- One (1) year non-hierarchical composite of device success and no need for HF hospitalization or HF hospitalization equivalent.
- Individual patient success (6 months and 1 year) defined as device success and all of the following:
    - No rehospitalizations or reinterventions for HF (includes HF hospitalization equivalents, new listing for heart transplant, need for VAD or CRT)
    - NYHA class improvement by at least 1 level from baseline
    - KCCQ improvement >10 vs. baseline
    - 6MWT improvement >50 meters vs. baseline
- Days alive and out of hospital at one (1) year.

13.1.3 Analysis of Baseline Characteristics

Subject demographics, risk factors, angiographic, echocardiographic and procedural characteristics will be summarized. These will be presented as the mean and standard deviation for continuous variables and as frequencies and percentages for discrete variables.

13.1.4 Analysis of Endpoints

Discrete endpoint variables will be presented in tabular format presenting the frequency and percent of each outcome. Continuous variables will be reported by providing their N, mean, median standard deviation, minimum and maximum values.

For the primary endpoint, a Kaplan-Meier curve will be presented that shows time from procedure to first event. Subjects will be censored on the date of discontinuation or the final date used for the analysis, whichever occurs first. This same analysis will be used for each component of the primary endpoint which is defined as a secondary endpoint. Each endpoint that is time-dependent will use this type of analysis.

For binary outcomes, a one sample Exact binomial test will be used to compare each response rate to 0.5. For continuous variables that meet the assumption of normality, the change from baseline will be compared to baseline using a one sample t-test. If the assumption for normality is not met, then a Wilcoxon signed-rank test will be performed.

14 MONITORING

14.1 MONITORING METHODS

A study monitor (CRA) will be assigned by Neovasc to monitor the progress of the study. The study monitor will remain in close contact with each investigational center throughout the duration of the study to provide any needed materials (e.g., CRFs) or answer any questions. The study monitor will be responsible for reviewing CRFs and visiting each investigational center periodically to observe study progress and compliance with the study protocol by each center.

Monitoring visits will be scheduled throughout the duration of the study between the monitor and the Investigator at a mutually convenient and available time. These visits will ensure that the facilities are still acceptable, the protocol and investigational plan are being followed, the IRB/EC/REB has been notified of approved protocol changes as required, complete records are being maintained, appropriate timely reports have been made to the Sponsor and the IRB/EC/REB, device and device inventory are controlled and the Investigator is carrying out all agreed activities. Any personnel changes must be reported to the monitor immediately and a training program scheduled and documented. Monitoring will be conducted in accordance with each country's specific requirements.

To protect subject confidentiality, the subject's name must not appear anywhere on the CRFs, imaging media, or source documentation sent to the Sponsor. Each page should be identified with the subject's study ID number only. All other subject identifiers (e.g., medical record number, subject name, date of birth) are to be obscured.

14.2 MONITORING PLAN

Prior to patient enrollment, a study initiation visit will be completed at each investigational center to ensure the following:

1. IRB/EC/REB approval has been obtained and documented;

2. The Investigators and study personnel are appropriately trained and clearly understand the study;
3. The Investigators and study personnel accept the obligations incurred in undertaking this clinical investigation.

Interim Monitoring Visits will be conducted to ensure the following:

1. The study is being conducted in accordance with the protocol;
2. EC/IRB/REB requirements and applicable regulations are being followed;
3. Managing product supplies, and ensuring ongoing follow-up of open action items;
4. Resolution of all outstanding site action items.

Close-out visits are conducted at the end of the study to ensure the following:

1. Study documentation is complete;
2. Open action items are closed;
3. Record retention requirements are understood.

14.3 PROTOCOL DEVIATION(S)

A protocol deviation is defined as an event where the Investigator or center personnel did not conduct the study according to the clinical protocol (clinical investigation plan) or the Investigator Agreement. Investigators shall be required to obtain proper approval from the Sponsor before initiating deviations from the clinical protocol, except where necessary to protect the life or physical well-being of a subject in an emergency. Such approval shall be documented in writing and maintained in study files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control (e.g., subject did not attend scheduled follow-up visit, etc.), however the event is still considered a deviation.

Deviations shall be reported to the Sponsor regardless of whether medically justifiable, pre-approved by Neovasc, or taken to protect the subject in an emergency. Subject-specific deviations will be reported on the CRFs. Investigators will also adhere to procedures for reporting study deviations to their institutional review committee in accordance with their specific review committee's reporting policies and procedures.

For reporting purposes, deviations are classified as major or minor:

1. **Major deviation**
    a. Any deviation from patient inclusion and exclusion criteria unless approved by the CSC prior to enrollment.
    b. Any deviation from patient informed consent procedures.

c. Unauthorized use of an investigational device outside of the study or not compliant with the current IFU.

d. Unauthorized use of an investigational device by a physician who has not signed an Investigator Agreement.

2. Minor deviation

a. Deviation from a protocol requirement such as incomplete/inadequate subject testing procedures.

b. Follow-up performed outside specified time windows, etc.

The site will receive a list of study deviations on an annual basis as part of the Annual Progress Report and as part of the Final Report. The Sponsor will review all study protocol deviations and implement corrective action plans for those deviations and investigational sites when necessary.

14.4 COMMUNICATION PROCEDURES

During the course of the study, all correspondence (letters, telephone calls, emails and faxes) regarding the study must be maintained in the study binder provided by the Sponsor. This binder must be made available for monitoring visits or audits.

15 STUDY COMMITTEES

15.1 EXECUTIVE STEERING COMMITTEE

The ESC will be in charge of overall study design and conduct and will be composed of key opinion leaders in transcatheter valve replacement. The committee will meet by teleconference or in person as frequently as necessary, to monitor subject enrollment, clinical site progress, and protocol compliance. This committee will be responsible for reviewing the final results, determining the methods of presentation and publication, and selection of secondary projects and publications.

15.2 CLINICAL EVENT COMMITTEE/DATA AND SAFETY MONITORING BOARD

Given the open label single arm design of this feasibility study, a combined Clinical Events Committee/Data and Safety Monitoring Board (CEC/DSMB) will be established to adjudicate adverse events and monitor the safety of the study. The CEC/DSMB members will be independent of both Neovasc and the study Investigators and will meet regularly according to a schedule determined during the first CEC/DSMB meeting. The CEC/DSMB will have at least three (3) members and will include at least one cardiothoracic surgeon and one interventional cardiologist, and as needed, a neurologist.

The CEC/DSMB will be responsible for adjudicating endpoint-related events reported during the trial. All CEC/DSMB meeting minutes will remain strictly confidential, but open session minutes will be made available to regulatory authorities upon request.

At the onset of the study, the CEC/DSMB will detail explicit rules outlining the minimum amount of data required. These rules will be submitted to the Sponsor for final approval. Members are provided data summaries from the clinical study.

The CEC/DSMB will meet prior to initiation of enrollment and periodically or as needed if significant safety issues are identified. During the first meeting the CEC/DSMB will review, modify as needed, and approve the CEC/DSMB charters. The CEC/DSMB may establish criteria (i.e., stopping rules) for recommending study termination. The CEC/DSMB will review all adverse events, deaths, explants and unanticipated adverse device effects in relation to the role of the device. The CEC/DSMB data review is to detect evidence of early dramatic benefit or harm for subjects while the clinical study is in progress. The CEC/DSMB will be responsible for recommending if the trial should be terminated prior to study completion due to, but not limited to, the observation that the serious adverse events outweigh possible clinical benefit.

Additional duties may be assigned during execution of the study protocol that are unforeseen (e.g., input on protocol modifications).

15.3 CORE LABORATORIES

Core Laboratories will be utilized throughout the study for review of Angiography, CT, and Echocardiography.

15.4 CENTRAL SCREENING COMMITTEE

The CSC will review each potential subject in order to make a formal determination of whether the subject meets enrollment criteria for the study, taking into account the specific screening tests (see Section 8.4) as well as the overall suitability of the subject. The committee will include experts in transcatheter valve replacement from the fields of cardiothoracic surgery, interventional cardiology, CT, and echocardiography.

16 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 APPLICABLE REGULATIONS AND GUIDELINES

It is the responsibility of the Investigator(s) to comply with the requirements set forth in their country-specific and institutional regulations. Furthermore, the Investigator must comply with the requirements of the Declaration of Helsinki or with laws of the foreign country, whichever will afford greater protection to the subject.

The Investigator should also take into consideration guidelines applicable to the study population such as the AHA/ACC 2014 Guidelines on Valvular Heart Disease, and the ESC/EACTS 2012 Guidelines on Valvular Heart Disease.

16.2 DATA PROTECTION AND SUBJECT CONFIDENTIALITY

The confidentiality and privacy of subjects who volunteer to participate in the study will be protected to the fullest extent possible. Passwords are issued to appropriate personnel to ensure confidentiality and protection of the database by allowing variable levels of access to the computer system on a need to know basis. In addition, the study Investigator is responsible for maintaining confidentiality throughout the clinical study. The hard copies of the CRFs and source documentation are to be maintained in a secure area with limited access. All subject identifiers will be obliterated from all photocopies of source documents that have been removed from the site. Subject identifiers include, but are not limited to: subject's name, social security number, and medical/hospital number. All study documents will identify the subject by a subject study identification number assigned by the Sponsor.

16.3 INFORMED CONSENT AND REVIEW COMMITTEES

All subjects must provide written informed consent in accordance with the local clinical center's institutional review committee. A copy of the consent form from each center must be forwarded to Neovasc for review and approval prior to submitting it to the institutional review committee. Each center must provide the Sponsor with a copy of the clinical center's IRB/EC/REB approval letter (stating the study name, protocol revision being approved and an approval date) and the informed consent. IRB/EC/REB approvals for the continuation of the trial at each clinical site must also be forwarded to the Sponsor.

16.4 INVESTIGATOR RESPONSIBILITIES

16.4.1 GENERAL DUTIES

The Investigator shall ensure that all work and services described herein, or incidental to those described herein, shall be conducted in accordance with the highest standards of medical and clinical research practice and the applicable regulations. The Investigator will provide copies of the current study protocol to all staff responsible for study conduct. The role of the Principal Investigator is to implement and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety, and well-being of the subjects involved in the clinical investigation.

The Principal Investigator is responsible for obtaining and maintaining site IRB/EC/REB approval.

16.4.2 INVESTIGATOR RECORDS

The Principal Investigator will maintain the accurate, complete, and current records relating to participation in this clinical study. Study records including CRFs and supporting data (e.g., copies of all labs and diagnostic exams, signed Clinical Trial Agreement, protocols and protocol amendments, signed ICFs, device usage, IRB/EC/REB approval letters, IRB/EC/REB submissions, correspondence, including required reports, and other documents pertaining to the conduct of the study) must be kept on file by the Investigator. The Sponsor will ensure that all study sites are trained on the requirement to retain and archive all records pertaining to this clinical study as per the Clinical Trial Agreement and/or local/national regulations, whichever is longer.

If the Investigator(s) wishes to assign the files to someone else or remove them to another location, the Investigator should consult with the Sponsor in writing as to this change. Study files must be maintained in a known location until the Sponsor notifies the Investigator in writing that he/she may discard them.

16.4.3 INVESTIGATOR REPORTS

The Principal Investigator will prepare and submit the following accurate and complete reports to the Sponsor and institutional review committee in a timely manner:

- Unanticipated adverse device effects occurring during the study will be reported as soon as possible, but no later than 10 working days after the Principal Investigator first learns of the event.
- Withdrawal of institutional review committee approval will be reported to the Sponsor within five (5) working days of review committee withdrawal. Annual progress reports will be submitted to the institutional review committee.
- Deviation from the clinical protocol (clinical investigation plan) to protect the subject's life or physical well-being in an emergency will be reported to the Sponsor and the IRB/EC/REB within five (5) working days. Planned deviations from the clinical protocol (investigational plan) require prior approval from the Sponsor and as required from the IRB/EC/REB. Use of the TMVR study devices without informed consent will be reported to Neovasc and IRB/EC/REB within five (5) working days after the use occurs.
- A final written report is submitted to the Sponsor and the IRB/EC/REB within three months of completion or termination of the trial.
- Upon request by a reviewing IRB/EC/REB or the pertinent regulatory agencies, the Principal Investigator will provide current information about any aspect of the investigation.

16.5 SPONSOR RESPONSIBILITIES

16.5.1 GENERAL DUTIES

As the Sponsor of this clinical study, Neovasc has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the pertinent regulatory agencies. In this study, Neovasc will have primary responsibility and will delegate some responsibilities to (but not limited to) core labs and EDC vendors.

16.5.2 SELECTION OF INVESTIGATORS

Neovasc will select qualified Investigators and will ship investigational devices to participating Investigators fully trained for the clinical study (e.g., IFU, study manual, etc.). Neovasc will obtain signed study agreements and provide the Investigators with the information and supplies necessary to conduct the study.

16.5.3 MONITORING THE STUDY

The Sponsor will ensure compliance with the signed clinical trial agreement, the protocol (clinical investigation plan), the requirements of applicable regulations according to geographic investigational site location/jurisdiction, and any conditions of study approval by the regulatory authorities.

Neovasc will conduct an immediate investigation of any unanticipated adverse device effects (UADEs) and if an event is found to present an unreasonable risk to study subjects.

16.5.4 SPONSOR RECORDS

Neovasc will maintain accurate, complete, and current records relating to this clinical study. Study records include CRFs, signed clinical trial agreements, financial disclosures, protocols and protocol amendments, device usage, IRB/EC/REB approval letters and submissions, correspondence, including required reports, and other documents. The Sponsor will maintain study documentation during the study and for up to two (2) years (or as required by the applicable regulatory requirements) after the study is terminated or completed, or the study records are no longer required to support a regulatory submission. Storage of the study records may be designated to a third party.

16.5.5 SPONSOR REPORTS

The Sponsor will prepare and submit the following accurate and complete reports to the investigational site's IRB/EC/REB and the pertinent regulatory agencies in a timely manner:

- Unanticipated adverse device effects reported by an investigational site will be evaluated and the IRB/EC/REB and the pertinent regulatory agencies will be informed of the results of the evaluation no later than 10 working days after the Sponsor first learns of the event.
- Withdrawal of IRB/EC/REB approval will be reported to all IRB/EC/REBs and the pertinent regulatory agencies within five (5) working days of receipt of withdrawal of approval.
- Withdrawal of the pertinent regulatory agencies' approval will be reported to investigational centers and IRB/EC/REBs within five (5) working days after receiving the notice of approval withdrawal.
- A current Investigator list will be submitted to the pertinent regulatory agencies at six (6) month intervals, if applicable.
- Progress reports will be submitted to the IRB/EC/REBs at least annually and to the pertinent regulatory agencies as required.
- A final written report is to be completed and submitted to the IRB/EC/REBs and the pertinent regulatory agencies within six months after completion or termination of the trial.
- Use of the investigational TMVR device without informed consent will be reported to regulatory authorities within five (5) working days after notification of device use.
- Upon request by a reviewing IRB/EC/REB or the pertinent regulatory agencies, Neovasc will provide current information about any aspect of the investigation.

16.6 STUDY CHANGES

Changes in the protocol may be made only by written amendment agreed upon by the Sponsor, Investigator, and if pertinent, the IRB/EC/REB. As appropriate, Neovasc will submit changes in the protocol to the pertinent regulatory agencies and Investigators to obtain IRB/EC/REB re-approval.

16.7 STUDY SUSPENSION OR PREMATURE TERMINATION

16.7.1 STUDY

The study could be suspended or prematurely terminated for the following reasons, including but not limited to:

- Business decision by Sponsor
- DSMB recommendation due to safety concerns

16.7.2 SINGLE SITE

The study could be suspended or prematurely terminated at a clinical investigaton site for the following reasons, including but not limited to:

- Investigator or site noncompliance
- Change in study personnel

16.7.3 SUBJECT FOLLOW-UP

In the event that either the study or an investigation site are terminated, subjects should continue follow-up care with their primary cardiologist.

16.8 STUDY COMPLETION OR TERMINATION AND CLOSE-OUT

The Principal Investigator will be notified in writing upon termination/conclusion of the study. Neovasc retains the right to suspend or terminate this clinical study at any time.

16.9 AUDITS AND INSPECTIONS

In the event that audits are initiated by the Sponsor or national/international regulatory authorities, the Investigator shall allow access to the original medical records and provide all requested information.

16.10 PUBLICATION POLICY

The Sponsor and the Executive Steering Committee are committed to the timely and transparent dissemination of the trial results. A multicenter publication will be prepared for publication in a reputable scientific journal. The publication of the principal results from any single center experience within the trial is not allowed until the preparation and publication of the multicenter results. Exceptions to this rule require prior approval from Neovasc. For purposes of abstract presentation and publication, any secondary publications will be delegated to the appropriate principal authors, and final analyses and manuscript review for all multicenter data will require the approval of Neovasc.

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18 SCHEDULE OF STUDY ACTIVITIES AND TESTS

Test/Activity	Screening[1]	Baseline (-7–0 days)[2]	Procedure	Day 1	Discharge (or up to 10 days)[3]	30 Days (plus up to 7 days)	90 Days (± 14 days)	180 Days (± 21 days)	Annual (± 30 days)	Unscheduled Visit
Informed consent	X	X								
Physical exam (including neurological exam[4]) and subject interview	X	X		X	X	X	X	X	X	X
Pregnancy test (for ♀ of reproductive potential)	X	X								
Listing of current medications	X[11]	X	X[12]		X	X	X	X	X	X
NYHA class	X	X			X	X	X	X	X	X
Blood (serum) chemistry[5]	X	X		X	X	X	X	X	X	
CBC with differential	X	X		X	X	X	X	X	X	
Reticulocyte count		X		X	X	X	X	X	X	
PT/INR	X	X		X	X	X				
PTT	X	X		X						
Plasma free hemoglobin		X				X	X	X	X	
Haptoglobin		X				X	X	X	X	
NTProBNP or BNP[6]	X	X			X	X	X	X	X	
Troponin I or T		X		X						
Plasma sample[7]		X				X	X	X	X	
QoL survey (KCCQ)[8]		X				X	X	X	X	
NIH Stroke Scale[9] + Modified Rankin Scale[9]	X	X			X	X	X	X	X	
STS Risk Score/EuroSCORE II	X	X								
Canadian Study of Health and Aging (CSHA)	X	X							X	

Test/Activity	Screening[1]	Baseline (-7–0 days)[2]	Procedure	Day 1	Discharge (or up to 10 days)[3]	30 Days (plus up to 7 days)	90 Days (± 14 days)	180 Days (± 21 days)	Annual (± 30 days)	Unscheduled Visit
7-Point Clinical Frailty Scale									Year 1 only	
6 Minute Walk Test (6MWT)		X				X	X	X	X	
ECG	X	X		X	X	X	X	X	X	
TTE	X				X	X	X	X	X	
TEE	X		X[14]							
CT scan (dynamic)[10]	X					X				
Angiogram	X[13]		X							
Cine			X[14]			X				
Radiation monitoring			X[15]			X[16]				
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	X

Footnotes:

1 Screening procedures must be done no more than three months prior to the proposed procedure date, except as specifically noted in the protocol
2 Any testing conducted at the screening visit within seven days of the procedure may be utilized as baseline data and does not have to be repeated for the baseline visit
3 Discharge should be at the time of discharge or at day 10, whichever is earlier
4 If a stroke, TIA, or change in neurological status has occurred, a neurological exam should be performed by a neurologist
5 Glucose, Na, K, Cl, SGOT/AST, SGPT/ALT, BUN, Creatinine, Albumin, LDH, Alkaline Phosphatase
6 The test that is completed at the time of screening, either NTProBNP or BNP, should be collected throughout the duration of the study
7 Optional test dependent on site (EC/IRB/REB) approvals and subject approval/consent
8 Questionnaire completed by the subjects
9 Personnel conducting the mRS and NIHSS must have completed certification before conducting each exam
10 Dynamic CT of the chest with contrast (without contrast in those with eGFR < 40 ml/min)
11 Medication list to include review of guideline directed medical therapy (GDMT) for heart failure
12 Listing of medications administered during procedure
13 Angiogram may be collected within six months of the planned procedure date
14 TEE and Cine during the procedure should be recorded
15 Including all fluoroscopy time and radiation exposure
16 Examination for radiation injury

19 ABBREVIATIONS AND DEFINITIONS

ADE	Adverse Device Effect
AE	Adverse Event
ACC	American College of Cardiology
ACS	Acute Coronary Syndrome
ACT	Activated Clotting Time
AHA	American Heart Association
ARO	Academic Research Organization
BARC	Bleeding Academic Research Consortium
CAD	Coronary Artery Disease
CBC	Complete Blood Cell Count
CDRH	Center for Devices and Radiological Health
CDMS	Clinical Data Management System
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CIP	Clinical Investigation Plan
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate (monitor)
CRF	Case Report Form
CRO	Contract Research Organization
CSC	Central Screening Committee
CSHA	Canadian Study of Health and Aging
CT	Computed Tomography
cTn	Cardiac Troponin
CTS	Cardiothoracic Surgeon
DAPT	Dual Antiplatelet Therapy
DSMB	Data and Safety Monitoring Board
EACTS	European Association of Cardio-Thoracic Surgery
EC	Ethics Committee
ESC	Executive Steering Committee or European Society of Cardiology

FDA	Food and Drug Administration
GCP	Good Clinical Practices
GDMT	Guideline Directed Medical Therapy
GI	Gastrointestinal
GLP	Good Laboratory Practices
HF	Heart Failure
IC	Interventional Cardiologist
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IDE	Investigational Device Exemption
IFU	Instructions for Use
IRB	Institutional Review Board
ISO	International Standards Organization
ITT	Intent-to-Treat
LBBB	Left Bundle Branch Block
LV	Left Ventricle
MedDRA®	Medical Dictionary for Regulatory Activities
MACCE	Major Adverse Cardiac and Cerebrovascular Event
MACE	Major Adverse Cardiac Event
MI	Myocardial Infarction
MR	Mitral Regurgitation
MV	Mitral Valve
mRS	Modified Rankin Score
MVARC	Mitral Valve Academic Research Consortium
MVR	Mitral Valve Replacement
NIHSS	National Institutes of Health Stroke Scale
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
POBA	Plain Old Balloon Angioplasty
PROM	Preoperative Risk of Mortality

PVD	Peripheral Vascular Disease
QoL	Quality of Life
RBC	Red Blood Cells
REB	Research Ethics Board
RV	Right Ventricle
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
6MWT	Six Minute Walk Test
TAMI	Transapical Mitral Valve Implantation
TEE	Transesophageal Echocardiogram
TIA	Transient Ischemic Attack
TMVR	Transcatheter Mitral Valve Replacement
TMVS	Tiara™ Mitral Valve System
TR	Tricuspid Regurgitation
TTE	Transthoracic Echocardiogram
U	Units
UADE	Unanticipated Adverse Device Effect
ULN	Upper Limit of Normal
VARC-2	Valve Academic Research Consortium-2
VKA	Vitamin K Antagonist

20 STUDY ENDPOINT DEFINITIONS

The following definitions used for the trial are adapted from VARC-2[10]and MVARC[12].

Term	Definition
Acute Kidney Injury[10]	**Stage 1** Increase in serum creatinine to 150–199% (1.5–1.99 × increase compared with baseline) OR increase of ≥ 0.3 mg/dl (≥ 26.4 mmol/l) OR urine output < 0.5 ml/kg/h for ≥ 6 but < 12 h **Stage 2** Increase in serum creatinine to 200–299% (2.0–2.99 × increase compared with baseline) OR urine output < 0.5 ml/kg/h for ≥ 12 but < 24 h **Stage 3** Increase in serum creatinine to ≥ 300% (> 3 × increase compared with baseline) OR serum creatinine of ≥ 4.0 mg/dl (≥ 354 mmol/l) with an acute increase of at least ≥0.5 mg/dl (44 mmol/l) OR urine output < 0.3 ml/kg/h for ≥ 24 h OR anuria for ≥ 12 h NOTE: Patients receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria.
Arrhythmias and Conduction System Disturbances[12]	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 in the post-procedural period is recommended to maximize the detection of 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

Term	Definition
	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.
Bleeding[12]	MVARC (Primary 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** 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-hour 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,

Term	Definition
	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. ***MVARC Footnotes:*** **Modified with permission from VARC-2[12].* *†"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 BARC Bleeding Scale[12]	**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)

Term	Definition
	• 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 • 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. ***MVARC Footnotes:*** **Modified with permission from VARC-2[12].* *†"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).*

Term	Definition
Death/Mortality[12]	**I. Classification of All-Cause 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** • 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

Term	Definition
Device Success[10]	Absence of procedural mortality AND Correct positioning of a single prosthetic heart valve into the proper anatomical location AND Intended performance of the prosthetic heart valve (no prosthesis – patient mismatch) AND No moderate or severe prosthetic valve regurgitation
Hospitalization[10]	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. **I. Heart failure hospitalization:** Both of the following additional criteria are present: i. Symptoms, signs and/or laboratory evidence of worsening heart failure ii. Administration of intravenous or mechanical heart failure therapies 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. Noncardiovascular hospitalization:** not due to heart failure or other cardiovascular causes, as defined above
Myocardial Infarction[12]	**I. Periprocedural MI (≤48 h after the index procedure)** • In patients with normal baseline CK-MB (or cTn): o The peak CK-MB measured within 48 h of the procedure rises to ≥10 the local laboratory ULN plus new ST-

Term	Definition
	segment elevation or depression of ≥1 mm in ≥2 contiguous leads (measured 80 ms after the J-point), or to ≥5 ULN with new pathological Q waves in ≥2 contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 h of the PCI rises to ≥70 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. • In patients with elevated baseline CK-MB (or cTn): o The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level plus, new ECG changes as described. **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: A. Symptoms of ischemia B. ECG changes indicative of new ischemia (new ST-segment or T-wave changes or newLBBB) 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** MI is defined in pathology as myocardial cell death due to prolonged ischaemia. After the onset of myocardial ischaemia, histological cell death is not immediate, but takes a finite period of time to develop—as little as 20 min, or less in some animal models.4 It takes several hours

Term	Definition
	before myocardial necrosis can be identified by macroscopic or microscopic post-mortem examination. Complete necrosis of myocardial cells at risk requires at least 2– 4 h, or longer, depending on the presence of collateral circulation to the ischaemic zone, persistent or intermittent coronary arterial occlusion, the sensitivity of the myocytes to ischaemia, pre-conditioning, and individual demand for oxygen and nutrients.2 The entire process leading to a healed infarction usually takes at least 5– 6 weeks. Reperfusion may alter the macroscopic and microscopic appearance
Stroke and TIA[12]	**Diagnostic criteria** I. Acute episode of a focal or global neurological deficit with at least 1 of the following: o Change in the level of consciousness o Hemiplegia, hemiparesis, numbness, or sensory loss affecting 1 side of the body o Dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke II. 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** I. 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 II. TIA: duration of a focal or global neurological deficit <24 h and neuroimaging does not demonstrate a new hemorrhage or infarct Confirmation of the diagnosis of stroke or TIA requires at least 1 of the following I. Neurologist or neurosurgical specialist, or II. Neuroimaging procedure (CT scan or brain MRI) **Stroke/TIA timing classification** I. Periprocedural if it occurs within 30 days of the intervention, or if beyond 30 days in the patient not yet discharged. A

Term	Definition
	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. II. Nonperiprocedural if it occurs beyond 30 days after the intervention and after the patient has been discharged. **Stroke/TIA etiology classification** I. Ischemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue II. Hemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage III. Undetermined: if there is insufficient information to allow categorization as ischemic or hemorrhagic **Stroke severity is further classified as** I. Disabling stroke: an mRS score ≥2 at 90 days plus an increase in ≥1 mRS category from the pre-stroke baseline II. 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 according to a certification process.
Access Site and Vascular Complications[12]	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

Term	Definition
	requiring surgery or resulting in amputation or irreversible end-organ damage, or iv. Unplanned endovascular or surgical interventions resulting in death; lifethreatening, 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) <u>II. Cardiac structural complications due to access-related issues</u> **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

21 STUDY-REQUIRED TEST AND EXAMINATION DEFINITIONS

21.1 DEFINITION OF GRADE D SYMPTOMATIC SEVERE MITRAL REGURGITATION

2014 AHA/ACC Valvular Heart Disease Guideline[4] Definition

	Primary (Degenerative)	Secondary (Functional)
Valve Anatomy	1. Severe mitral valve prolapse with loss of coaptation or flail leaflet 2. Rheumatic valve changes with leaflet restriction and loss of central coaptation 3. Prior Infective Endocarditis 4. Thickening of leaflets with radiation heart disease	1. Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet 2. Annular dilation with severe loss of central coaptation of the mitral leaflets
Valve Hemodynamics	1. Central jet MR >40% LA or holosystolic eccentric jet MR 2. Vena contracta ≥0.7 cm 3. Regurgitant volume ≥60 mL 4. Regurgitant fraction ≥50% 5. ERO ≥0.40 cm^2 6. Angiographic grade 3–4+	1. ERO ≥0.20 cm^2 2. Regurgitant volume ≥30 mL 3. Regurgitant fraction ≥50%
Hemodynamic Consequences/ Associated Cardiac Findings	1. Moderate or severe LA enlargement 2. LV enlargement 3. Pulmonary hypertension present	1. Regional wall motion abnormalities with reduced LV systolic function 2. LV dilation and systolic dysfunction due to primary myocardial disease
Symptoms	1. Decreased exercise tolerance 2. Exertional dyspnea	1. HF symptoms due to MR persist even after revascularization and optimization of medical therapy 2. Decreased exercise tolerance 3. Exertional dyspnea

*Several valve hemodynamic criteria are provided for assessment of MR severity, but not all criteria for each category will be present in each patient. Categorization of MR severity as mild, moderate, or severe depends on data quality and integration of these parameters in conjunction with other clinical evidence.

ERO indicates effective regurgitant orifice; IE, infective endocarditis; LA, left atrium/atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD; left ventricular end-systolic dimension; and MR, mitral regurgitation

21.2 STS SCORE CALCULATION/DEFINITIONS

http://riskcalc.sts.org/de.aspx

The Society of Thoracic Surgeons' risk models predict the risk of operative mortality and morbidity after adult cardiac surgery on the basis of patient demographic and clinical variables. The models are primarily used to adjust for case mix when comparing outcomes across institutions with different patient populations. Such comparisons are provided in the Database reports received by STS Database participants. The STS models are also used by physicians and patients as tools for understanding the possible risks of surgery. As these risks are solely statistical estimates, they should be supplemented by the professional judgment of the patients' healthcare provider, particularly their cardiac surgeon.

Surgical Procedures
The STS currently has three risk models: CABG, Valve, and Valve + CABG. The models apply to seven specific surgical procedure classifications:

CABG model
1. Isolated Coronary Artery Bypass (CABG Only)

Valve model
2. Isolated Aortic Valve Replacement (AV Replace)
3. Isolated Mitral Valve Replacement (MV Replace)
4. Isolated Mitral Valve Repair (MV Repair)

Valve+CABG model
5. Aortic Valve Replacement + CABG (AV Replace + CABG)
6. Mitral Valve Replacement + CABG (MV Replace + CABG)
7. Mitral Valve Repair + CABG (MV Repair + CABG)

NOTE: A predicted risk value will NOT be calculated for any procedure that does not fall into one of these precisely defined categories.

21.1 CSHA CLINICAL FRAILTY

(A global clinical measure of fitness and frailty in elderly people)

Canadian Study of Health and Aging (CSHA) Clinical Frailty Scale [9]

1. **Very fit** – Robust, active, energetic, well motivated and fit; these people commonly exercise regularly and are in the most fit group for their age
2. **Well** – Without active disease, but less fit than people in category 1
3. **Well, with treated comorbid disease** – Disease symptoms are well controlled compared with those in category 4
4. **Apparently vulnerable** – Although not frankly dependent, these people commonly complain of being "slowed up" or have disease symptoms
5. **Mildly frail** – With limited dependence on others for instrumental activities of daily living
6. **Moderately frail** – Help is needed with both instrumental and non-instrumental activities of daily living
7. **Severely frail** – Completely dependent on others for the activities of daily living, or terminally ill

IADL (Instrumental Activities of Daily Living)	ADL (Activities of Daily Living)
• Activities required to live in the community • Meal preparation • Ordinary housework • Managing finances • Managing medications • Phone use • Shopping • Transportation	• Mobility in bed • Transfers • Locomotion inside and outside the home • Dressing upper and lower body • Eating • Toilet use • Personal hygiene • Bathing

21.1 NYHA, MRS, NIHSS, 6MWT, AND KCCQ

New York Heart Association Classification (NYHA)	**Class I** Patients with cardiac disease but without resulting limitations of physical activity. **Class II** Patients with cardiac disease resulting in slight limitation of physical activity. Patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea, or anginal pain. **Class III** Patients with cardiac disease resulting in marked limitation of physical activity. Patients are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation dyspnoea, or anginal pain. **Class IV** Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.
Modified Rankin Scale (mRS)	0 No symptoms at all 1 No significant disability despite symptoms; able to carry out all usual duties and activities 2 Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance 3 Moderate disability; requiring some help, but able to walk without assistance 4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance 5 Severe disability; bedridden, incontinent, and requiring constant nursing care and attention 6 Death Prior to conducting the mRS, the assessor must be certified in completing this neurological assessment.

National Institutes of Health Stroke Scale (NIHSS)	The National Institutes of Health Stroke Scale, or NIH Stroke Scale (NIHSS) is a tool to objectively quantify the impairment caused by a stroke. The NIHSS is composed of 11 items, each of which scores a specific ability. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score. Prior to conducting the NIHSS, the asssor must be certified in completing this neurological assessment.
6 Minute Walk Test (6MWT)	This test measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes. It evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism. The self-paced 6MWT assesses the submaximal level of functional capacity. Most patients do not achieve maximal exercise capacity during the 6MWT; instead, they choose their own intensity of exercise and are allowed to stop and rest during the test. The 6MWT detailed in the "*ATS Statement: Guidelines for the Six-Minute Walk Test*[13]" should be followed to conduct this examination.
The Kansas City Cardiomyopathy Questionnaire (KCCQ)	The Kansas City Cardiomyopathy Questionnaire is a 23-item, self-administered instrument that quantifies physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge, and quality of life. This questionnaire should be given to the subject to complete on his or her own.