HeartMate 3 Registry:

Evaluating the HeartMate 3™ with Full MagLev Technology in a Post-Market Approval Setting (ELEVATE™)

Sponsor:
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REVISION HISTORY

Version	Date	Revision Summary
NA	09-Jan-2015	Original Protocol for Kazakhstan.
1	08-Mar-2015	Original Protocol for Europe.
1.1	16-Dec-2015	Addition of retrospective enrollments (implemented only in centers where subjects were not enrolled consecutively).
2.0	05-Dec-2016	Addition of anonymized data collection for subjects with outcome prior consenting (implemented only in centers where subjects implanted with HM3 expired prior having the chance of signing the Informed Consent Form).
3.0	20-Jun-2019	Subject follow up extended to 5 years. Introduction of a minimum compliance threshold and early study termination. SAE reporting timelines requirement added. Revised sponsor from Thoratec to St Jude Medical/Abbott. Revised patient to subject throughout the document

COMPLIANCE STATEMENT

This clinical investigation will be conducted in accordance with this Clinical Investigation Plan, the Declaration of Helsinki, ISO14155:2011 standards and the appropriate local legislation(s). The most stringent requirements, guidelines or regulations must always be followed. The conduct of the clinical investigation will be approved by the appropriate Ethics Committee (EC) of the respective clinical site and as specified by local regulations.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

6MWT ..... Six-Minute Walk Test
AAA..... Abdominal Aortic Aneurysm
ACE ..... Angiotensin Converting Enzyme
ADE ..... Adverse Device Effect
AE ..... Adverse Event
AI ..... Aortic Insufficiency
AICD ..... Automatic Internal Cardiac Defibrillator
ALT ..... Alanine Aminotransferase
ARB ..... Angiotensin Receptor Blocker
AST..... Aspartate Aminotransferase
AV ..... Aortic Valve
BNP ..... B-type Natriuretic Peptide
BSA..... Body Surface Area
BUN ..... Blood Urea Nitrogen (Urea, blood)
CE..... Conformité Européenne
CI ..... Cardiac Index
CK..... Creatine Kinase
CNS ..... Central Nervous System
COPD..... Chronic Obstructive Pulmonary Disease
CPB ..... Cardiopulmonary Bypass
CRF ..... Case Report Form
CRP ..... C-reactive Protein
CRT ..... Cardiac Resynchronization Therapy
CV..... Cardiovascular
CVP ..... Central Venous Pressure
EC..... Ethics Committee
ECG ..... Electrocardiogram
eCRF..... Electronic Case Report Form
EDC ..... Electronic Data Capture
EEG ..... Electroencephalogram
eGFR ..... Glomerular Filtration Rate
EQ-5D-5L..... EuroQol Health Utility Index
FEV_1.....Forced Expiratory Volume in one second
FVC…….Forced Vital Capacity
GCP ..... Good Clinical Practices
HF ..... Heart Failure
HM3 ..... HeartMate 3
HR..... Heart Rate
Hs-CRP..... High Sensitivity C-reactive Protein
IABP..... Intra Aortic Balloon Pump
ICD..... Internal Cardiac Defibrillator
ICF ..... Informed Consent Form
INR..... International Normalized Ratio
INTERMACS….Interagency Registry for Mechanically Assisted Circulatory Support
LDH..... Lactic Acid Dehydrogenase
LOS..... Length of Stay
LV ..... Left Ventricle
LVAD..... Left Ventricular Assist Device
LVAS..... Left Ventricular Assist System

LIST OF ABBREVIATIONS

LVEDD ..... Left Ventricular End Diastolic Diameter
LVEF ..... Left Ventricular Ejection Fraction
LVESD ..... Left Ventricular End Systolic Diameter
MB ..... Myocardial Band
MCS ..... Mechanical Circulatory Support
MR ..... Mitral Regurgitation
NT-ProBNP ..... N terminal B-type natriuretic peptide
NYHA ..... New York Heart Association
PHgb ..... Plasma Free Hemoglobin
PRBC ..... Packed Red Blood Cells
PT ..... Prothrombin Time
PTT ..... Partial Thromboplastin Time
PVD ..... Peripheral Vascular Disease
PVR ..... Pulmonary Vascular Resistance
RV ..... Right Ventricle
RVAD ..... Right Ventricular Assist Device
SAE ..... Serious Adverse Event
SBP ..... Systolic Blood Pressure
SHFM ..... Seattle Heart Failure Model
Thoratec ..... Thoratec Corporation
TR ..... Tricuspid Regurgitation
VAD ..... Ventricular Assist Device
WBC ..... White Blood Cells

TABLE OF APPENDICES

1 INTRODUCTION

The purpose of this post-market registry is to collect data and evaluate the real-world experience of the HeartMate 3 Left Ventricular Assist System (HM3 LVAS) in a post-approval setting. The data collection will be similar to the HM3 CE Mark study in order to be able to compare the pre-market to post-market results and to continue to have a more robust HM3 dataset.

This post-market registry will be initiated after receipt of the CE Mark and commercial approval of the HM3 LVAS.

This protocol is being amended to include long term follow-up of the ELEVATE Registry Study subjects. The subjects that are still implanted with the HM3 LVAD after completing the 2-year follow up will be re-consented and their follow-up will be extended for an additional 3 years (a total of 5 years of follow-up post-implant). This will allow for the evaluation of late occurring adverse events, long-term quality of life, functional status and will provide more information on the real world treatment with the HM3 LVAD of advanced heart failure subjects.

The original sponsor of this study and manufacturer of the HM3 LVAS, Thoratec Corporation, was acquired by St. Jude Medical on October 8, 2015. St Jude Medical was further acquired by Abbott on January 4, 2017. St. Jude Medical is currently the study sponsor however, due to the recent acquisition, there may be reference to Abbott in this document.

2 REGISTRY DESIGN

2.1 Scope

This registry will include all subjects that receive the HM3 LVAS in the post-market setting. This registry will include up to 500 subjects in up to 50 centers. Consecutive subject enrollment (at least 5 consecutive subjects) is recommended to minimize subject selection bias and provide a more robust dataset. A log should be maintained of any subjects that are not included in this Registry and reasons for non-inclusion.

2.2 Subject Eligibility

Any subject that is determined to meet the HM3 commercially approved labelling indication and that is implanted or has been implanted with the HM3 and has consented to the registry data collection can be enrolled in this registry.

2.2.1 Special circumstances when consent cannot be obtained

To ensure that survival is accurately reported in this Registry, for subjects that have had an outcome prior to consenting no consent will be obtained and the following data will be collected:

- Duration (days) of HM3 support;
- Subject outcome (transplanted, explanted or expired). If the subject expired, the cause of death.

For subjects that have had an outcome after the 24 months visit and prior to reconsenting for the long term follow up, the same data will be collected retrospectively.

2.3 Follow-up

Subjects will be followed in the registry to 24 months post-implant or outcome (transplanted, explanted for recovery or expired), whichever occurs first.

Subjects who provide consent for the extended follow up period (CIP Version 3.0 and newer) will be followed in the registry through 60 months post implant or until they meet another study outcome (transplanted, explanted for recovery or expired), whichever occurs first.

2.4 Design

This is a prospective observational registry, subjects can be enrolled retrospectively from the date HM3 received the CE Mark and prospectively until the sample size is reached.

2.4.1 Data collection

Data collection will include pre-implant, implant and post-implant at hospital discharge, 6 months, 12 months and 24 months.
For those subjects who provide consent for the extended follow up period, additional follow ups are planned at 36, 48 and 60 months while the subject is being supported on the HM3 LVAS.

2.4.2 Long Term Follow-Up

The follow-up period is extended from 24 to 60 months post-implant. Subjects will be reconsented to allow data collection in the additional follow ups.
If subject is consented after they have had their standard of care 36 or 48 month visits, data will be collected restrospectively and the subject will be scheduled prospectively for the next protocol required follow-up.
The follow-up extension will allow the evaluation of late occurring adverse events, long-term quality of life, functional status and provide more information on the real-world experience of the HM3 LVAS in a post-approval setting.

2.4.3 Early Study Termination

The Sponsor will monitor the study compliance through the follow-ups beyond 24 months and every effort will be made to maintain a high level of compliance.
If the overall study compliance (calculated as a proportion between subjects active in the study vs the total amount of subjects still on HM3 support) or the followup visit compliance (calculated as a proportion between expected and received follow up data) cannot be maintained to at least 85% the study will be terminated prematurely by the sponsor. Subjects who have experienced an outcome as transplant, explant or death are not included in this compliance calculation.

2.4.4 Endpoints

The major endpoints that will be analyzed (at 2 years and at 5 years only for subjects who consent to participate in the extended Follow up) include:

- Outcomes
- Quality of Life as measured by the EuroQoL-5D-5L
- Functional status as measured by the Six Minute Walk Test (6MWT) and New York Heart Association (NYHA) Classification.
- Frequency and incidence of pre-defined anticipated adverse event rates
- Frequency and incidence of device malfunction rates
- Frequency and incidence of reoperations
- Frequency and incidence of rehospitalizations

3 DATA COLLECTION

Subjects will be followed per the hospital standard of care. Assessments collected in this registry are considered standard of care at most institutions. Please refer to Section 7 for the Visit Schedule.

3.1 Database

The data will be collected via an electronic data capture system (EDC). This database is maintained and administered by Abbott. Users will have unique usernames and passwords, and the user list will be maintained by a Sponsor's administrator for all study personnel.

3.2 Pre-implant Demographics and Profile

The standard demographics of age, gender, and subject-described ethnicity will be recorded. Heart failure etiology, duration, and standard prognostic factors will be collected along with hemodynamic, laboratory and echocardiographic parameters closest to the time of implant. Co-morbidities and previous cardiovascular medical history will be also included. The subjects functional and clinical status will be assessed by NYHA classification, INTERMACS Subject Profile and the 6 minute walk test. The subject will also be asked to complete the quality of life assessment.

3.3 Implant

The elements which characterize the HM3 device and describe the implant procedure will be recorded in the Registry database. Note that the implant form that is provided in the pump packaging should be completed following usual commercial device reporting procedures.

3.4 Post-Implant Follow-up

Refer to Section 7.0 for the visit schedule. Any subject related events (adverse events, reoperations, rehospitalizations, outcomes) should be reported as they occur. The date of discharge will be collected. The six minute walk and quality of life assessment will be administered at aseline and every follow-up as of 6 months visit.

3.4.1 Adverse Events (AE)

Adverse Events should be reported in the Registry database as they occur. The INTERMACS adverse event definitions will be used and can be found in Appendix 1.

Note that the usual commercial device reporting procedures should be followed for any non-adverse events device malfunctions and product complaints. A Sponsor representative must be informed of any product related complaints.

In the Registry adverse events are defined as any unfavorable and unintended sign, or symptom or disease temporally associated with the device. The AEs will be categorized as related to the device (Adverse Device Effect) or not.

In addition all adverse events will be further categorized as serious or not. Serious adverse events (SAEs) are defined as those causing death, fetal distress, fetal death or congenital abnormality or birth defect, or a life-threatening illness or injury that results in permanent disability, requires hospitalization, or prolongs a hospitalization, and/or requires intervention to prevent permanent injury or damage.

All SAEs will be categorized as related to the device (Serious Adverse Device Effect) or not and must be reported to the Sponsor no later than 3 calendar days from the day the site personnel became aware of the event (or as per the investigative site's local requirements, if the requirement is more stringent than those outlined).

3.4.2 Reoperations

Any cardiac or non-cardiac surgical or operative procedures (including pump exchanges/replacements) that occur during the follow-up period will be collected.

3.4.3 Rehospitalizations

Rehospitalizations and the associated reasons will be captured during the follow-up period.

3.4.4 Outcomes

The subjects's outcome during the follow-up period will be captured and should be reported as occurs. The outcomes include: transplanted, explanted, expired, or withdrawn.
The subject retains the right to withdraw from the registry data collection at any time. Should the subjects elect to withdraw from the registry data collection, the reason for withdrawal should be documented.

4 DATA ANALYSIS

The endpoints were selected to evaluate the same parameters as those collected in the HM3 CE Mark Study.

In general, continuous data will be presented as the number of subjects, mean with standard deviation, median and minimum and maximum values. Categorical data will be reported as frequencies and percentages. Survival data will be presented using the Kaplan-Meier product limit method.

Statistical analysis will be performed using SAS version 9.1 or higher.

5 SUBJECT SAFETY

5.1 Risks

This registry will be initiated upon HM3 LVAS commercial approval therefore there is no added procedural risk to subjects participating in this post-market registry. No risk or procedures beyond those required for routine standard of care will be imposed. The data collected for this registry are mostly from medical chart abstraction. The only exception is the collection of functional capacity data and QoL data. These data are standard of care for heart failure subjects receiving VADs and are not considered greater than minimal risk.

There is always the risk of loss of confidentiality. However, safeguards, policies and procedures are in place to keep personal health information confidential. No published or unpublished report or visual or speaking presentation about the study will include any material that will identify a subject participating in this registry.

5.2 Mitigations

As the device will be commercially approved at the initiation of this post-market registry, mitigations and treatment for any adverse events associated with VAD therapy would be per the current practice standards and standards of care as determined by the treating physician.

5.3 Benefits

There is no direct benefit to the heart failure subjects who participate in this post-market registry. However, future heart failure subjects may benefit from the knowledge gained through this registry.

6 ETHICAL REQUIREMENTS

6.1 Informed Consent for Data Collection

Prior to data entery into the registry the subject or legal representative must sign an informed consent. The informed consent must inform the subject that the subject's data will be entered into a database outside of the hospital. The informed consent must have prior approval from the Ethics Committee (EC).
The site is responsible for keeping the original signed informed consent form on file.

6.2 Ethics Committee Review

Before initiation of the registry, EC approval of the protocol and the informed consent form (ICF) must be obtained. Any modifications made to the ICF should be sent to the Sponsor for approval, prior to submitting to the EC. Copies of the EC submission and approval, including the approved informed consent form, should be forwarded to the Sponsor prior to the enrollment of subjects into the registry. Copies of all submissions to and correspondence from the Ethics Committee (approvals and disapprovals) must be maintained on file at the site.

6.3 Data Handling and Record Keeping

Sponsor and/or its affiliates will maintain documentation of the systems and procedures used in data collection for the duration of the clinical investigation.

CRF data collection will be performed through a secure web portal and only authorized personnel will access the Electronic Data Capture (EDC) system using a unique username and password to enter, review or correct data. Passwords and electronic signatures will be strictly confidential.

The data will be subjected to consistency and validation checks within the EDC system and supplemental review by the Sponsor.

At the conclusion of the clinical investigation, completed CRF images with the date-and-time stamped electronic audit trail indicating the user, the data entered, and any reason for change (if applicable) will be provided to the investigational sites.

For the duration of the clinical investigation, the Investigator will maintain complete and accurate documentation including, but not limited to, medical records, clinical investigation progress records, laboratory reports, CRFs, signed ICFs, device accountability records (if applicable), correspondence with the IRB/EC and clinical investigation monitor/Sponsor, adverse event reports, and information regarding subject discontinuation or completion of the clinical investigation.

6.4 Protection of Personally Identifiable Information

The Sponsor respects and protects personally identifiable information collected or maintained for this clinical investigation.

The Sponsor implements technical and physical access controls to ensure that Personal Information is accessible only to and processed only on a 'need to know' basis, including periodic review of access rights, and revocation of access when an individual's employment is terminated or the individual transitions to a role that does not require access to Personal Information, and appropriate restrictions on physical access to premises, facilities, equipment, and records containing Personal Information.

The Sponsor requires the investigational sites to transfer into Sponsor's data management systems only Information (key-coded) necessary to conduct the Clinical Investigation, such as the subject's medical condition, treatment, dates of treatment, etc. The Sponsor discloses as part of the clinical investigation informed consent process that some Sponsor representatives still may see Personal Information at the participating sites for technical support of the participating physicians on the device implant or procedures, monitoring and quality control purposes. Confidentiality of Personal Information will be observed by all parties involved at all times throughout the clinical investigation. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data.

The Sponsor data management systems and processes were designed, developed, and tested according to industry standards to appropriately safeguard Confidential Information (including any Personal Information) against unauthorized access and/or interference by third parties, intrusion, theft, destruction, loss or alteration. Clinical Investigation data are encrypted in transit and at rest.

The Sponsor maintains a Privacy Incident procedure that complies in all respects with Applicable Law and industry best practices.

6.5 Data Management Plan

A Data Management Plan (DMP) will describe procedures used for data review, data cleaning, and issuing and resolving data discrepancies. If appropriate, the DMP may be updated throughout the duration of the clinical investigation. All revisions will be tracked and document controlled.

6.6 Source Documentation

Regulations and GCP require the Investigator to maintain information in the subject's original medical records that corroborates data collected on the CRFs. In order to comply with these regulatory requirements/GCP, the following information should be included in the subject record at a minimum and if applicable to the clinical investigation:

- Medical history/physical condition of the subject before involvement in the clinical investigation sufficient to verify CIP entry criteria
- Dated and signed notes on the day of entry into the clinical investigation referencing the Sponsor, CIP number, subject ID number and a statement that informed consent was obtained
- Dated and signed notes from each subject visit (for specific results of procedures and exams)
- Adverse events reported and their resolution, including supporting documents, such as discharge summaries, catheterization laboratory reports, ECGs, and lab results including documentation of site awareness of SAEs and of investigator assessment of device relationship for SAEs.
- Subject's condition upon completion of or withdrawal from the clinical investigation
- Any other data required to substantiate data entered into the CRF
- Subject reported outcome measures may be completed using CRF worksheets. These serve as the source documentation.

6.7 Case Report Form Completion

Primary data collection based on source-documented hospital and/or clinic chart reviews will be performed clearly and accurately by site personnel trained on the CIP and CRF completion. The investigator will ensure accuracy, completeness, legibility and timeliness of the data reported to the Sponsor on the CRFs and in all required reports.

Data on CRFs will be collected for all subjects that are enrolled into the clinical investigation. Only authorized site personnel will be permitted to enter the CRF data through the EDC system deployed by the Sponsor. An electronic audit trail will be used to track any subsequent changes of the entered data.

6.8 Record Retention

The Sponsor and Investigator/Site will archive and retain all documents pertaining to the clinical investigation as per the applicable regulatory record retention requirements. The Investigator must obtain permission from Sponsor in writing before destroying or transferring control of any clinical investigation records.

6.9 Monitoring

The Sponsor will perform remote monitoring to ensure data is submitted in a timely manner, that the data is sensical and queries are resolved. Ongoing communication with the site will be performed through written correspondence and telephone conversations.

7 HM3 POST-MARKET REGISTRY VISIT SCHEDULE

NOTE: Subject must have HM3 implanted and signed informed consent prior to data entry in registry

	Consent	Pre-Implant	Implant	Discharge	Month 6 (+/- 1 month)	Month 12 (+/- 1 month)	Month 24 (+/- 1 month)	Month 36 (+/- 1 month)	Month 48 (+/- 1 month)	Month 60 (+/- 1 month)	As occurs
Consent	X										
Long Term Follow-Up Consent	X										
Demographics		X									
Medical & CV History		X									
Vital Signs		X		X	X	X	X	X	X	X	
Hemodynamic Measurements		X									
Laboratory Assessments		X			X	X	X	X	X	X	
Echocardiogram		X			X	X	X	X	X	X	
EQ-5D-5L		X			X	X	X	X	X	X	
NYHA Classification		X			X	X	X	X	X	X	
INTERMACS Profile		X									
Six Minute Walk Test		X			X	X	X	X	X	X	
Current Cardiovascular Medications		X									
Implant Data/CPB Time/Blood Products/Concurrent Procedures			X								
Current Subject Status					X	X	X	X	X	X	
Pump Parameters				X	X	X	X	X	X	X	
Subject Outcome											X
Long Term Follow-Up Subject Outcome											X
Rehospitalizations											X
Adverse Events											X
Device Malfunctions											X
Reoperations/Operative Procedures (incl pump replacements/exchanges)											X

APPENDIX 1: ANTICIPATED ADVERSE EVENT DEFINITIONS (INTERMACS DEFINITIONS)

Major Bleeding
An episode of SUSPECTED INTERNAL OR EXTERNAL BLEEDING that results in one or more of the following:
a. Death,
b. Reoperation,
c. Hospitalization,
d. Transfusion of red blood cells as follows:
1. If transfusion is selected, then apply the following rules:

During first 7 days Post-implant
1. Adults (≥ 50 kg): ≥ 4U packed red blood cells (PRBC) within any 24 hour period during first 7 days post-implant.

After 7 days Post-implant
2. Any transfusion of packed red blood cells (PRBC) after 7 days following implant with the investigator recording the number of units given. (Record number of units given per 24 hour period).

Note: Hemorrhagic stroke is considered a neurological event and not as a separate bleeding event.

Cardiac Arrhythmias
Any documented arrhythmia that results in clinical compromise (e.g., diminished VAD flow, oliguria, pre-syncope or syncope) that requires hospitalization or occurs during a hospital stay. Cardiac arrhythmias are classified as 1 of 2 types:
1) Sustained ventricular arrhythmia requiring defibrillation or cardioversion.
2) Sustained supraventricular arrhythmia requiring drug treatment or cardioversion.

Pericardial Fluid Collection
Accumulation of fluid or clot in the pericardial space that requires surgical intervention or percutaneous catheter drainage. This event will be subdivided into those with clinical signs of tamponade (e.g. increased central venous pressure and decreased cardiac/VAD output) and those without signs of tamponade.

Device Malfunctions *
Device malfunction denotes a failure of one or more of the components of the MCS system which either directly causes or could potentially induce a state of inadequate circulatory support (low cardiac output state) or death. A failure that was iatrogenic or recipient-induced will be classified as an Iatrogenic/Recipient-Induced Failure.

Device failure should be classified according to which components fails as follows:
1) Pump failure (blood contacting components of pump and any motor or other pump actuating mechanism that is housed with the blood contacting components). In the special situation of pump thrombosis, thrombus is documented to be present within the device or its conduits that result in or could potentially induce circulatory failure.
2) Non-pump failure (e.g., electric power supply unit, batteries, controller, interconnect cable)

***Note: Device Malfunctions will be collected via the Sponsor's commercial product event complaint procedure and not in the Registry database. All product related events should be reported to a Sponsor's representative.**

Hemolysis
A plasma-free hemoglobin value that is greater than 40 mg/dl, in association with clinical signs associated with hemolysis (e.g., anemia, low hematocrit, hyperbilirubinemia) occurring after the first 72 hours post-implant. Hemolysis related to documented non-device-related causes (e.g. transfusion or drug) is excluded from this definition.

Hepatic Dysfunction
An increase in any two of the following hepatic laboratory values (total bilirubin, aspartate aminotransferase/AST and alanine aminotransferease/ALT) to a level greater than three times the upper limit of normal for the hospital, beyond 14 days post-implant (or if hepatic dysfunction is the primary cause of death).

Hypertension
New onset blood pressure elevation greater than or equal to 140 mm Hg systolic or 90 mm Hg diastolic (pulsatile pump) or 110 mm Hg mean pressure (rotary pump).

Major Infection
A clinical infection accompanied by pain, fever, drainage and/or leukocytosis that is treated by anti-microbial agents (non-prophylactic). A positive culture from the infected site or organ should be present unless strong clinical evidence indicates the need for treatment despite negative cultures. The general categories of infection are listed below:

Localized Non-Device Infection
Infection localized to any organ system or region (e.g. mediastinitis) without evidence of systemic involvement (see sepsis definition), ascertained by standard clinical methods and either associated with evidence of bacterial, viral, fungal or protozoal infection, and/or requiring empirical treatment.

Percutaneous Site and/or Pocket Infection
A positive culture from the skin and/or tissue surrounding the drive line or from the tissue surrounding the external housing of a pump implanted within the body, coupled with the need to treat with antimicrobial therapy, when there is clinical evidence of infection such as pain, fever, drainage, or leukocytosis.

Internal Pump Component, Inflow or Outflow Tract Infection
Infection of blood-contacting surfaces of the LVAD documented by positive site culture.

Sepsis
Evidence of systemic involvement by infection, manifested by positive blood cultures and/or hypotension.

Myocardial Infarction
Two categories of myocardial infarction will be identified:

Peri-Operative Myocardial Infarction
The clinical suspicion of myocardial infarction together with CK-MB or Troponin > 10 times the local hospital upper limits of normal, found within 7 days following VAD implant together with ECG findings consistent with acute myocardial infarction. (This definition uses the higher suggested limit for serum markers due to apical coring at the time of VAD placement, and does

not use wall motion changes because the apical sewing ring inherently creates new wall motion abnormalities.)

Non-Perioperative Myocardial Infarction
The presence at > 7 days post-implant of two of the following three criteria:

a) Chest pain which is characteristic of myocardial ischemia,
b) ECG with a pattern or changes consistent with a myocardial infarction, and
c) Troponin or CK (measured by standard clinical pathology/laboratory medicine methods) greater than the normal range for the local hospital with positive MB fraction (≥ 3% total CK). This should be accompanied by a new regional LV or RV wall motion abnormality on a myocardial imaging study.

Neurologic Dysfunction
Any new, temporary or permanent, focal or global neurological deficit ascertained by a standard neurological examination (administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests and consultation note). The examining physician will **distinguish** between a transient ischemic attack (TIA), which is fully reversible within 24 hours (and without evidence of infarction), and a stroke, which lasts longer than 24 hours (or less than 24 hours if there is evidence of infarction). Each neurological event must be subcategorized as:

1) Transient Ischemic Attack (acute event that resolves completely within 24 hours with no evidence of infarction)
2) Ischemic or Hemorrhagic Cerebral Accident/CVA (event that persists beyond 24 hours or less than 24 hours associated with infarction on an imaging study.

Psychiatric Episode
Disturbance in thinking, emotion or behavior that causes substantial impairment in functioning or marked subjective distress requiring intervention. Intervention is the addition of new psychiatric medication, hospitalization, or referral to a mental health professional for treatment. Suicide is included in this definition.

Renal Dysfunction
Two categories of renal dysfunction will be identified:

Acute Renal Dysfunction
Abnormal kidney function requiring dialysis (including hemofiltration) in Subjects who did not require this procedure prior to implant, or a rise in serum creatinine of greater than 3 times baseline or greater than 5 mg/dL (in children, creatinine greater than 3 times upper limit of normal for age) sustained for over 48 hours.

Chronic Renal Dysfunction
An increase in serum creatinine of 2 mg/dl or greater above baseline, or requirement for hemodialysis sustained for at least 90 days.

Respiratory Failure
Impairment of respiratory function requiring reintubation, tracheostomy or (for Subjects older than age 5 years) the inability to discontinue ventilatory support within six days (144 hours) post-VAD implant. This excludes intubation for reoperation or temporary intubation for diagnostic or therapeutic procedures.

Right Heart Failure
Symptoms and signs of persistent right ventricular dysfunction [central venous pressure (CVP) > 18 mmHg with a cardiac index <2.3 L/min/m2 in the absence of elevated left atrial/pulmonary capillary wedge pressure (greater than 18 mmHg), tamponade, ventricular arrhythmias or pneumothorax] requiring RVAD implantation; or requiring inhaled nitric oxide or inotropic therapy for a duration of more than 1 week at any time after LVAD implantation.

Arterial Non-CNS Thromboembolism
An acute systemic arterial perfusion deficit in any non-cerebrovascular organ system due to thromboembolism confirmed by one or more of the following:

1) Standard clinical and laboratory testing
2) Operative findings
3) Autopsy findings

This definition excludes neurological events.

Venous Thromboembolism Event
Evidence of venous thromboembolic event (e.g. deep vein thrombosis, pulmonary embolism) by standard clinical and laboratory testing.

Wound Dehiscence
Disruption of the exposed surfaces of a surgical incision, excluding infectious etiology, and requiring surgical repair.

Other
An event that causes clinically relevant changes in the Subject's health (e.g. cancer).

APPENDIX 2: INTERMACS PROFILE/CLASSIFICATION

INTERMACS Profile*	Definition
1	Critical cardiogenic shock describes a patient who is "crashing and burning", in which a patient has life-threatening hypotension and rapidly escalating inotropic pressor support, with critical organ hypoperfusion often confirmed by worsening acidosis and lactate levels.
2	Progressive decline describes a patient who has been demonstrated "dependent" on inotropic support but nonetheless shows signs of continuing deterioration in nutrition, renal function, fluid retention, or other major status indicator. Patient profile 2 can also describe a patient with refractory volume overload, perhaps with evidence of impaired perfusion, in whom inotropic infusions *cannot be maintained* due to tachyarrhythmias, clinical ischemia, or other intolerance.
3	Stable but inotrope dependent describes a patient who is clinically stable on mild-moderate doses of intravenous inotropes (or has a temporary circulatory support device) after repeated documentation of failure to wean without symptomatic hypotension, worsening symptoms, or progressive organ dysfunction (usually renal). It is critical to monitor nutrition, renal function, fluid balance, and overall status carefully in order to distinguish between a patient who is truly stable at Patient Profile 3 and a patient who has unappreciated decline rendering this person a Patient Profile 2. This patient may be either at home or in the hospital.
4	Resting symptoms describes a patient who is at home on oral therapy but frequently has symptoms of congestion at rest or with ADL. He or she may have orthopnea, shortness of breath during ADL such as dressing or bathing, gastrointestinal symptoms (abdominal discomfort, nausea, poor appetite), disabling ascites or severe lower extremity edema. This patient should be carefully considered for more intensive management and surveillance programs, by which some may be recognized to have poor compliance that would compromise outcomes with any therapy.
5	Exertion Intolerant describes a patient who is comfortable at rest but unable to engage in any activity, living predominantly within the house or housebound. This patient has no congestive symptoms, but may have chronically elevated volume status, frequently with renal dysfunction, and may be characterized as exercise intolerant.
6	Exertion Limited also describes a patient who is comfortable at rest without evidence of fluid overload, but who is able to do some mild activity. Activities of daily living are comfortable and minor activities outside the home such as visiting friends or going to a restaurant can be performed, but fatigue results within a few minutes of any meaningful physical exertion. This patient has occasional episodes of worsening symptoms and is likely to have had a hospitalization for heart failure within the past year.
7	Advanced NYHA Class 3 describes a patient who is clinically stable with a reasonable level of comfortable activity, despite history of previous decompensation that is not recent. This patient is usually able to walk more than a block. Any decompensation requiring intravenous diuretics or hospitalization within the previous month should make this person a Patient Profile 6 or lower.

*Stevenson, L.W. et al. INTERMACS Profiles of Advanced Heart Failure: The Current Picture, J Heart Lung Transplant. 2009 28(6): 535-541

APPENDIX 3: NYHA CLASSIFICATION

Classification	Definition
I	Cardiac disease without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea or anginal pain.
II	Cardiac disease resulting in slight limitation of physical activity. Subjects are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
IIIA	Cardiac disease resulting in marked limitations of physical activity. Subjects are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IIIB	Cardiac disease resulting in marked limitations of physical activity. Subjects are comfortable at rest. Mild physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	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.

APPENDIX 4: 6MWT ELEVATE

SIX-MINUTE HALLWAY WALK TEST INSTRUCTIONS

Purpose
The purpose of the 6-Minute Hallway Walk test (6MWT) is to walk as far as possible for 6-minutes, without running or jogging, as a way of measuring functional status.

Preparing for the test

1. Establish a 30-meter walking course in an enclosed corridor, preferably free of distractions and close to a wall so that if needed, the Subject may rest against it during the test (note: a treadmill is not an acceptable alternate method for this study).
2. Mark the course at 3-meter intervals using a method unnoticeable to the Subject.
3. Place noticeable markers at either end of the 30-meter course to indicate the turnaround points.
4. The distance covered during the preceding walk test will not be revealed to the Subject during the study.
5. A warm up prior to the test should not be performed.

Explaining the test procedure to the Subject

1. Clearly explain to the Subject what is required of him/her using the following instructions verbatim:

   THE PURPOSE OF THIS TEST IS TO WALK AS FAR AS POSSIBLE FOR SIX-MINUTES. YOU WILL START FROM THIS POINT AND FOLLOW THE HALLWAY TO THE MARKER AT THE END, THEN TURN AROUND AND WALK BACK. WHEN YOU ARRIVE BACK AT THE STARTING POINT, YOU WILL GO BACK AND FORTH AGAIN. YOU WILL GO BACK AND FORTH AS MANY TIMES AS YOU CAN IN THE SIX-MINUTE PERIOD. IF YOU NEED TO, YOU ARE PERMITTED TO SLOW DOWN, TO STOP, AND TO REST AS NECESSARY. YOU MAY LEAN AGAINST THE WALL WHILE RESTING, BUT RESUME WALKING AS SOON AS YOU ARE ABLE. HOWEVER, THE MOST IMPORTANT THING ABOUT THE TEST IS THAT YOU COVER AS MUCH GROUND AS YOU POSSIBLY CAN DURING THE SIX MINUTES. I WILL KEEP TRACK OF THE NUMBER OF LAPS YOU COMPLETE AND I WILL LET YOU KNOW WHEN THE SIX MINUTES ARE UP. WHEN I SAY STOP, PLEASE STAND RIGHT WHERE YOU ARE.

   DO YOU HAVE ANY QUESTIONS ABOUT THE TEST?

   PLEASE EXPLAIN TO ME WHAT YOU ARE GOING TO DO.

2. The Subject will re-state the instructions. If the Subject does not seem to understand, repeat the entire instructions.

   Conducting the test

   1. Position the Subject at the starting line.
   2. Repeat the sentence:

      THE MOST IMPORTANT THING ABOUT THE TEST IS THAT YOU COVER AS MUCH GROUND AS YOU POSSIBLY CAN DURING THE SIX MINUTES.

      ARE YOU READY?

      START NOW, OR WHENEVER YOU ARE READY.

3. Start the timer as soon as the Subject takes the first step.
4. During the test, the walking pace of the Subject should not be influenced. The test supervisor must walk behind the Subject – do not walk with, rush up behind, or rush past the Subject.
5. Each time the Subject returns to the starting line, record the lap.
6. While walking, encourage the Subject at one minute intervals with the following phrases:

1 minute:	YOU ARE DOING WELL. YOU HAVE 5 MINUTES TO GO.
2 minutes:	KEEP UP THE GOOD WORK. YOU HAVE 4 MINUTES TO GO.
3 minutes:	YOU ARE DOING WELL. YOU ARE HALFWAY DONE.
4 minutes:	KEEP UP THE GOOD WORK. YOU HAVE ONLY 2 MINUTES LEFT.
5 minutes:	YOU ARE DOING WELL. YOU HAVE ONLY ONE MINUTE TO GO.

7. The Subject should be spoken to only during the 1-minute encouragements; no response should be made to the Subject's questions about the time and distance elapsed.
   a. If the Subject is not concentrating on the walking, the Subject can be reminded at a 1-minute mark:

      THIS IS A WALKING TEST, TALKING WILL UTILIZE YOUR ENERGY RESERVE AND INTERFERE WITH YOUR PERFORMANCE.

1. When only 15 seconds remain, state:

   IN A MOMENT I AM GOING TO TELL YOU TO STOP. WHEN I DO, STOP RIGHT WHERE YOU ARE AND I WILL COME TO YOU.

9. When the timer reads 6-minutes, instruct the Subject to STOP and walk over to him/her. Consider bringing a chair if the Subject appears exhausted. Mark the spot where the Subject stopped.

   If the Subject wishes to stop walking during the test
   If the Subject is slowing down and expresses that he/she wants to pause, keep the timer running and state:

   REMEMBER, IF YOU NEED TO, YOU MAY LEAN AGAINST THE WALL UNTIL YOU CAN CONTINUE WALKING AGAIN.

   If the Subject wishes to stop before the 6-minutes are complete and refuses to continue (or you decide that he/she should not continue), provide a chair for the Subject to sit on and discontinue the test. Record the distance completed, the time the test was stopped and the reason for pre-maturely stopping.

   Immediately after the test
   1. Total the number of completed laps and add the additional distance covered in the final partial lap. Record the distance walked to the nearest meter.
   2. Observe the Subject sitting in a chair for at least 10 minutes after the test is completed.