HeartMate™ 3
CE Mark Study Long Term Follow-up
Clinical Investigation Plan

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REVISION HISTORY

Version	Date	Revision Summary	Originator	Release Date
1	11/Mar/2016	Original Protocol	Laura Damme	11/Mar/2016

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LIST OF ABBREVIATIONS

6MWT .....Six-Minute Walk Test
ACC .....American College of Cardiology
ACE .....Angiotensin Converting Enzyme
ADE .....Adverse Device Effect
AE.....Adverse Event
AHA .....American Heart Association
AI .....Aortic Insufficiency
AICD .....Automatic Internal Cardiac Defibrillator
AIMDD .....Active Implantable Medical Device Directive
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
CFR .....Code of Federal Regulations
CI .....Cardiac Index
CIP.....Clinical Investigation Plan
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
CSA .....Clinical Study Agreement
CV.....Cardiovascular
CVP .....Central Venous Pressure
DT.....Destination Therapy
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
EU.....European Union
FEV_1.....Forced Expiratory Volume in one second
FVC…….Forced Vital Capacity
FDA .....U.S. Food and Drug Administration
GCP.....Good Clinical Practices
H_0.....Null Hypothesis
H_A .....Alternative Hypothesis
HF .....Heart Failure

LIST OF ABBREVIATIONS

HM II .....HeartMate II
HM 3 .....HeartMate 3
HR .....Heart Rate
Hs-CRP.....High Sensitivity C-reactive Protein
IABP .....Intra Aortic Balloon Pump
IB .....Investigator Brochure
ICD .....Internal Cardiac Defibrillator
ICH .....International Conference On Harmonization
ICF.....Informed Consent Form
IFU.....Instructions For Use
INTERMACS.....Interagency Registry for Mechanically Assisted Circulatory Support
INR .....International Ratio
LDH .....Lactic Acid Dehydrogenase
LOS .....Length of Stay
LV .....Left Ventricle
LVAD .....Left Ventricular Assist Device
LVAS .....Left Ventricular Assist System
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
NB.....Notified Body
NT-ProBNP.....N terminal B-type natriuretic peptide
NYHA.....New York Heart Association
OMM.....Optimal Medical Management
PHgb.....Plasma Free Hemoglobin
PI .....Principal Investigator
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
TR.....Tricuspid Regurgitation
USADE .....Unanticipated Serious Adverse Device Effect
VAD .....Ventricular Assist Device
WBC .....White Blood Cells
WMA.....World Medical Association

TABLE OF APPENDICES

STUDY SYNOPSIS	
Device	HeartMate 3 Left Ventricular Assist System (LVAS); The HeartMate 3 LVAS is commercially approved in the European Union (CE Mark approval received October 8, 2015) and in Kazakhstan.
Indications for Use	The HeartMate 3 LVAS(HM3) is intended to provide long term hemodynamic support in Patients with advanced, refractory left ventricular heart failure. It is intendedeither for temporary support, such as a bridge to cardiac transplantation (BTT) or as permanent destination therapy (DT). The HeartMate 3 LVAS is intended for use inside or outside the hospital.
Study Design	The study will be a single arm, prospective, multi-center, non-blinded and non-randomized study, intended to report on the long term use of the HeartMate 3 LVAS in those patients that completed the 2-year follow-up in the HeartMate 3 CE Mark study.
Study Population	Patients with advanced refractory left ventricular heart failure who were implanted with HeartMate 3 in the CE Mark Study and continue to be ongoing with the HeartMate 3 LVAS after the CE Mark Study 2 year follow-up will be enrolled in this study.
Study Objective	The study objective is to report the long term survival and incidence of adverse events in the patients who were implanted with HM3 in the CE Mark Study and continue to be ongoing with the HeartMate 3 LVAS after the CE Mark Study 2 year follow-up.
Study Endpoints	The following will be evaluated: 1. Survival: Patient outcomes and survival over time will be reported 2. Quality of Life as measured by the EuroQoL (EQ-5D-5L) 3. Functional status as measured by the Six Minute Walk Test (6MWT) and New York Heart Association (NYHA) classification 4. Frequency and incidence of pre-defined anticipated Adverse event rates 5. Frequency and incidence of device malfunction rates 6. Frequency and incidence of reoperations 7. Frequency and incidence of rehospitalizations 8. Survival free of debilitating stroke (Modified Rankin Score > 3).
Sample Size	The study will include the ongoing CE Mark study patients that have consented to continue the long term follow-up data collection.
Study Duration	Patients will be followed for 3 years in this study; from the time of completing the 2 year follow-up in the HeartMate 3 CE Mark study to 5 years post-implant or outcome (transplant, explant or death), whichever occurs first.
Inclusion Criteria	1) Patient or legal representative has signed Informed Consent Form (ICF) 2) Patient was enrolled in the HeartMate 3 CE Mark Study and continues to be supported with the HeartMate 3 LVAS
Exclusion Criteria	1) Patient does not consent to continued data collection.
Study Follow-up Intervals	Months 36, 48 and 60 post-implant.
Anticipated Adverse Events	Adverse events will be reported using INTERMACS Definitions : Major bleeding, Cardiac Arrhythmias, Pericardial fluid collection, Device malfunctions, Hemolysis, Hepatic dysfunction, Major Infection (Localized non-device infection, percutaneous site and/or pocket infection, internal pump component, inflow or outflow tract infection, sepsis), Myocardial infarction, Neurologic dysfunction, psychiatric episode, renal dysfunction, Arterial Non-CNS thromboembolism, Venous thromboembolism event, Wound dehiscence, Other adverse event.

STUDY SYNOPSIS	
Statistical Analysis	Long term data analyses including survival, adverse events, functional status and quality of life will be performed when all patients have been followed for 3, 4 and 5 years post HeartMate 3 CE Mark study implant. The 5 year survival of the HeartMate 3 patients will be compared against the INTERMACS data cohort which was used for the HeartMate 3 CE Mark study 6-month data analysis. In general, continuous data will be presented as the number of patients, 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, as well as the percentage of patients who successfully reach the pre-defined study endpoint. Every effort will be made to collect all required data. Missing secondary endpoints will not be imputed. Statistical analysis will be performed using SAS version 9.1 or higher
Number of Sites	Up to 10 centers

1 INTRODUCTION

The HeartMate 3 CE Mark study was conducted to evaluate the performance and safety of the HeartMate 3 Left Ventricular Assist System (HM 3 LVAS) in patients with advanced refractory left heart failure. A total of 50 patients were enrolled at 10 clinical centers in 6 countries between June 25, 2014 and November 27, 2014. The study met its 6-month primary study endpoint on May 26, 2015 after which time the data was submitted for CE Mark approval. The CE Mark for the HeartMate 3 LVAS was obtained October 8, 2015. The HM3 LVAS is approved for commercial use in the European Union and Kazakhstan, but remains investigational in Canada and Australia. The 6-month study results werepublished in the Journal of American College of Cardiology on December 15, 2015.[12]

On October 8, 2015, Thoratec Corporation, the sponsor of the HeartMate 3 CE Mark Study, was acquired by St. Jude Medical.

This purpose of this study is to continue the long term follow-up of the HeartMate 3 CE Mark Study patients. Those patients that are still ongoing after completing the 2-year follow-up in the CE Mark study will be enrolled into this study and followed for an additional 3 years (a total of 5 years of follow-up for the CE Mark study patients). This will allow for the evaluation of late adverse events, long-term quality of life, functional status and provide more information on the *in vivo* reliability of the device. The long term follow-up will be reported in the post-market clinical surveillance report in compliance with MedDev 2.12-2:2012[10] and GHT/SG5/N4[8].

2 INDICATIONS FOR USE

The indication for use in the HeartMate 3 LVAS CE Mark labelling is: The HeartMate 3 LVAS is intended to provide long term hemodynamic support in patients with advanced refractory left ventricular heart failure. It is intended either for temporary support, such as a bridge to cardiac transplantation (BTT), or as permanent destination therapy (DT). The HeartMate 3 LVAS is intended for use inside or outside the hospital.

3 DEVICE DESCRIPTION AND THEORY OF OPERATION

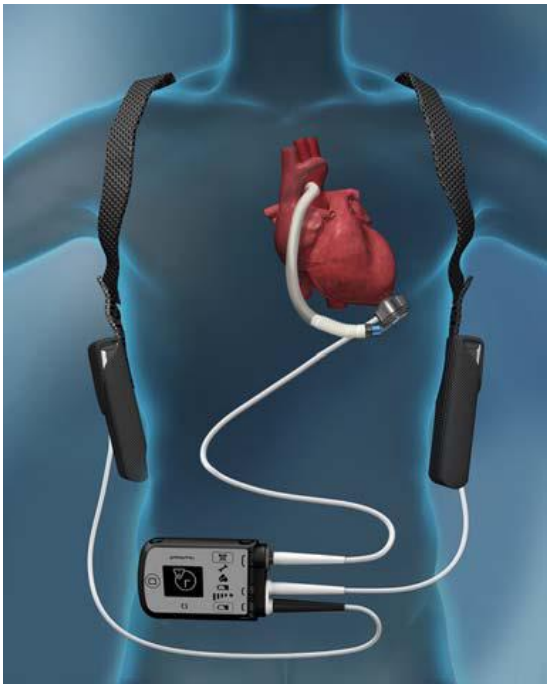
The HeartMate 3 Left Ventricular Assist System (LVAS) is a set of equipment and materials that together comprise a medical device designed to provide therapeutic benefit to those afflicted with advanced heart failure. In service, the LVAS assumes some or all of the workload of the left ventricle, thereby restoring the patient's systemic perfusion while palliating the underlying pathology. The LVAS features a Left Ventricular Assist Device (LVAD), a centrifugal magnetically levitated pump intended for long-term implantation in such patients, an extracorporeal Controller, plus all of the features, controls, attachments, interfaces, power sources, supporting equipment, labeling, and tools required to achieve the desired therapeutic benefit.

The LVAS may be used in either of two configurations. First, line power may be utilized through the Power Module or Mobile Power Unit to run the LVAD indefinitely, convenient for sedentary or sleeping periods. Second, portable Battery power may be utilized for limited periods, convenient for active periods. Due to the bifurcation of the Patient

Cable, switching among these configurations or from one set of Batteries to another (as when one set has been depleted and a fully charged set is available) may be accomplished without interrupting LVAS function. Whenever the Power Module is used a System Monitor may also be used as a means of viewing operating conditions, changing operating parameters, and manipulating stored data.

The HeartMate 3 LVAD is part of the LVAS. See Figure 1. The LVAD is a blood pump intended for long-term implantation in the thorax of patients afflicted with advanced heart failure. The LVAD is surgically connected to the patient's circulatory system via an Inflow Cannula placed into the left ventricular apex, and an Outflow Graft anastomosed to the ascending aorta. Detailed surgical, patient management and storage and handling instructions can be found in the HeartMate 3 Instructions For Use (IFU).

Figure 1 – HeartMate 3 System during Battery-powered Operation



The HeartMate 3 LVAD contains an Inflow Cannula, a Pump Cover, a Lower Housing, a Screw Ring to attach the Pump Cover to the Lower Housing, a Motor, the Outflow Graft, and a Pump Cable.

The HeartMate 3 Controller is also part of the Left Ventricular Assist System (LVAS). The Controller is an extracorporeal interface device that receives power from the Power

Module, Mobile Power Unit, or portable Batteries, and appropriately delivers that power to the LVAD. It is the primary user interface and has several important functions:

- Operating condition display,
- Source of audible and visible alarms,
- Communication link for transferring event/period log and alarm information, and
- Battery backup in the case of full power disconnection.

The HeartMate 3 LVAD is assembled in St. Jude Medical's manufacturing facility in Zurich, Switzerland. All other HeartMate 3 components and accessories are manufactured at St. Jude Medical's manufacturing facility in Pleasanton, California, U.S.A. A complete list of HeartMate 3 LVAS components and accessories, including model and/or serial/lot numbers is included in the HeartMate 3 IFU.

4 DEVICE TESTING

The HeartMate 3 LVAD/LVAS is an implantable long-term support device/system. As such, it has been designed in compliance with all applicable EU and international standards[5,6,7,9]. The device/system has been subjected to a comprehensive verification and validation effort to ensure its safety including evaluation of biocompatibility, sterility and long term reliability and this was performed prior to the HeartMate 3 CE Mark clinical study. The device testing data was submitted to the Notified Body for the purpose of obtaining the CE Mark.

5 STUDY DESIGN

The study will be a single arm, prospective, multi-center, non-blinded and non-randomized study, intended to report on the long term use of the HeartMate 3 LVAS in those patients that completed the 2-year follow-up in the HeartMate 3 CE Mark study.

6 STUDY DURATION

Patients will be followed for 3 years in this study; from the time of completing the 2 year follow-up in the HeartMate 3 CE Mark study to 5 years post-implant or outcome (transplant, explant or death), whichever occurs first.

7 NUMBER OF CLINICAL SITES AND PATIENTS

A total of 50 patients at 10 centers were enrolled in the HeartMate 3 CE Mark Study. The patients that continue to be ongoing with the HeartMate 3 LVAS after the CE Mark Study 2 year follow-up will be enrolled in this study.

8 STUDY POPULATION

Patients with advanced refractory left ventricular heart failure who were implanted with HeartMate 3 in the CE Mark Study and continue to be ongoing with the HeartMate 3 LVAS after the CE Mark Study 2 year follow-up will be enrolled in this study.

9 CLINICAL STUDY OBJECTIVES

9.1 STUDY OBJECTIVE

The study objective is to report the long term survival and incidence of adverse events in the patients who were implanted with HeartMate 3 in the CE Mark Study and continue to be ongoing with the HeartMate 3 LVAS after the CE Mark Study 2 year follow-up.

9.2 STUDY ENDPOINTS

9.2.1 Survival

Patient outcomes and survival over time will be reported.

9.2.2 Quality of Life

Quality of Life as measured by the EuroQoL-5D-5L

9.2.3 Functional Status

Functional status as measured by the Six Minute Walk Test (6MWT).
Functional status as measured by New York Heart Association (NYHA) Classification.

9.2.4 Adverse Events

Frequency and incidence of pre-defined anticipated adverse event rates

9.2.5 Device Malfunctions

Frequency and incidence of device malfunction rates

9.2.6 Reoperations

Frequency and incidence of reoperations

9.2.7 Rehospitalizations

Frequency and incidence of rehospitalizations

9.2.8 Survival Free of Debilitating Stroke (Modified Rankin Score >3)

10 INCLUSION CRITERIA

1) Patient or legal representative has signed Informed Consent Form (ICF).
2) Patient was enrolled in the HeartMate 3 CE Mark Study and continues to be supported with the HeartMate 3 LVAS after the 2 year CE Mark study follow-up.

11 EXCLUSION CRITERIA

1) Patient does not consent to the continued data collection.

12 DATA ANALYSIS AND STATISTICAL ISSUES/JUSTIFICATION FOR STUDY DESIGN

12.1 SAMPLE SIZE

The study will include the ongoing CE Mark study patients that have consented to continue the long term follow-up data collection.

12.2 STATISTICAL ANALYSIS

Long term data analyses including survival, adverse events, functional status and quality of life will be performed when all patients have been followed for 3, 4 and 5 years post HeartMate 3 CE Mark study implant. The 5 year survival of the HeartMate 3 patients will be compared against the INTERMACS data cohort which was used for the HM3 CE Mark study 6-month data analysis.

In general, continuous data will be presented as the number of patients, 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, as well as the percentage of patients who successfully reach the pre-defined study endpoint.

Every effort will be made to collect all required data. Missing secondary endpoints will not be imputed.

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

12.2.1 Analysis Population

The ongoing CE Mark study patients that have consented to continue the long term follow-up data collection will be included in the analysis.

12.2.2 Study Hypothesis

This is an long-term observational study of the ongoing CE Mark study patients. Long term data analyses including survival, adverse events, functional status and quality of life will be performed when all patients have been followed for 3, 4 and 5 years post HeartMate 3 CE Mark study implant. The 5 year survival of the HeartMate 3 patients will be compared against the INTERMACS data cohort which was used for the HM3 CE Mark study 6-month data analysis.

12.2.3 Analyses of Study Endpoints

12.2.3.1 Survival

Overall survival will be analyzed using the product-limit method of Kaplan and Meier. A competing outcome analysis will also be performed.

12.2.3.2 Adverse Events

All pre-defined adverse events will be collected and reviewed to ensure accurate reporting. Tables will be created that show the relation to device, frequency and incidence of all adverse events, time to event, and the event rate per patient year of support. Tables will be created that show the incidence and event rates per patient year of support for all serious adverse events.

12.2.3.3 Device Malfunctions

All suspected device malfunctions of the HeartMate 3 LVAS will be reported. St. Jude Medical will ask that all explanted devices including their components be returned for analysis. Data on device

malfunctions will be analyzed and tables will be created that report the following:

- If the event is confirmed by analysis of the device by St Jude Medical engineers
- The component of the device involved (internal or external)
- Days to the malfunction
- Action(s) taken in response to the malfunction

12.2.3.4 Rehospitalization

Time to rehospitalization, frequency and the reason for rehospitalization will be reported. Time in and out of the hospital will also be reported.

12.2.3.5 Reoperations/Operative Procedures

Time to reoperation, frequency of reoperation, and the reason for the surgery will be reported.

12.2.3.6 Functional Status

Functional status will be measured using the New York Heart Association Functional Class (NYHA) and the Six Minute Walk Test (6MWT).

NYHA

Results will will be compared to baseline scores using Fisher's Exact Test.

Six Minute Walk Test

Patients may not be able to walk due to illness, especially at baseline. Patients unable to walk due to illness will receive a score of 0 meters. For all other reasons for missing data the score will remain missing and not included in the analysis. The distance walked will be compared to baseline distances using a paired t-test. All data will also be graphically presented.

12.2.3.7 Quality of Life

Quality of Life will be measured using the EQ-5D-5L. The EQ-5D-5L VAS and total score post-implant will be compared to baseline scores using a paired t-test. In addition, the percentage of each component of the EQ-5D-5L will be graphically presented over time.

12.2.4 Collection of Pump Log Files

Pump log files should be submitted to St. Jude Medical in association with a suspected device malfunction to assist in characterization of pump operation and system diagnostic purposes. No specific pre-defined analysis will be performed on this data.

12.2.5 Long Term Follow-up

Patients who complete the 5 year follow-up in this study will continue to be followed by their health care providers in accordance with the standard of care established by their healthcare provider.

12.3 WITHDRAWALS

Patients will be considered withdrawn from the study if:

- The patient withdraws their consent to participate in the study, or
- The patient has their HeartMate 3 permanently explanted or deactivated for reasons other than myocardial recovery, or
- The patient has their HeartMate 3 replaced with a LVAD other than a HeartMate 3

In all cases, the reason for withdrawal will be determined and an adverse event or device malfunction reported, if applicable. Patients who are withdrawn from the study will not be replaced. Patients who are withdrawn will be censored at the time of withdrawal in all survival analysis

13 ADVERSE EVENTS (AE) AND ADVERSE DEVICE EFFECT (ADE)

13.1 ADVERSE EVENTS/ADVERSE DEVICE EFFECT

Adverse Events are any unfavorable and unintended sign (including abnormal labs), or symptom or disease temporally associated with the device and whether or not related to the use of the device. Investigators are responsible for reporting required pre-defined AEs to the study sponsor in a timely manner by submitting AEs through the electronic data capture system (EDC), and for reporting AEs to their Ethics Committee (EC) as required.

All pre-defined AEs, including those occurring after discharge, will be reported and will be categorized as related to the device (Adverse Device Effect) or not.

INTERMACS definitions will be used for all anticipated adverse events. Anticipated adverse event definitions can be found in Appendix 1.

13.2 SERIOUS ADVERSE EVENT/SERIOUS ADVERSE DEVICE EFFECT

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. Investigators are responsible for reporting SAEs to the study sponsor in a timely manner (but no later than 24 hours after becoming aware of an SAE) by submitting SAEs through the electronic data capture system (EDC), and for reporting SAEs to their EC as required.

All SAEs will be reported and will be categorized as related to the device (Serious Adverse Device Effect) or not.

13.3 EARLY STUDY TERMINATION FOR SAFETY CONCERNS

St. Jude Medical will monitor all adverse events and device malfunctions throughout the trial. As this is a long term follow-up study, early study termination does not apply to this study.

14 UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECTS (USADE)

An unanticipated serious adverse device effect includes 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. Investigators are responsible for reporting any USADEs to St Jude Medical by telephone or email and through the electronic data capture system (EDC) as soon as the study site personnel are made aware of an event, but no later than 24 hours of becoming aware. Telephone reports concerning USADEs must be followed by a written report to St. Jude Medical within five (5) working days of the event. St. Jude Medical will review all malfunctions and determine if they are USADEs. St. Jude Medical will report all such effects to the appropriate regulatory bodies, in accordance with regulatory requirements.

In addition to reporting USADEs to the Study Sponsor, Investigators must report USADEs to their EC in accordance with local EC requirements.

15 STUDY PROCEDURES AND ASSESSMENTS

Special equipment is not required to conduct study procedures or assessments. Participating centers will utilize their own local laboratories for protocol required laboratory assessments, and will be instructed to follow their institutions requirements for maintenance and/or calibration of laboratory equipment. For EDC, a computer with 256Mb RAM, Intel II processor or higher, current version Internet Explorer Firefox or Chrome, and an available internet connection is required.

15.1 ENROLLMENT

Patients will be enrolled after the 2 year CE Mark study follow-up visit. Any events (e.g. adverse events, rehospitalizations, reoperations) that occur after the 2 year CE Mark study visit are intended to be captured in this long term follow-up study. Patients are considered enrolled upon signing of the informed consent for this follow-up study.

15.2 PATIENT FOLLOW-UP ASSESSMENTS

15.2.1 Clinic Follow-up: Month 36, 48 and 60 (+/- 2 month) Post-implant

The Patients must be seen for a clinic visit to assess the following:

1. Current patient status: whether the patient is ongoing on HeartMate 3 support
2. Patient outcome: whether or not the patient has been transplanted, explanted or expired
3. EQ-5D-5L
4. 6MWT
5. Pump Replacements/Explants/ Device Exchanges
6. Occurrence of AEs (date of the adverse event, determination of seriousness and/or relation to device, resolution of the adverse event)
7. Device Malfunctions
8. Laboratory assessments per standard of care
9. Driveline management assessment

10. Reoperations/Operative procedures
11. Rehospitalizations
12. NYHA Classification
13. Log files (pump period log, pump event log, controller period log, and controller event log) if a device malfunction is suspected should be submitted to St. Jude Medical.

For a detailed list of assessments and timelines, refer to the Study Visit Schedule in Section 32.

16 ANTICOAGULATION

Patients supported with the HeartMate 3 must be properly anticoagulated to decrease the possibility of thromboembolism. Anticoagulation guidelines are provided in the HeartMate 3 Instructions for Use (IFU).

17 INFECTION CONTROL GUIDELINES

It is recommended that the Patient Care and Management Guidelines developed for the HeartMate 3 LVAS are followed. Guidelines for infection control and driveline management are provided in the HeartMate 3 Instructions for Use (IFU).

18 POST-MORTEM EXAMINATION

All attempts to obtain permission for a full body autopsy should be made for patients that experience a death that is possiblydevice related. Performance of an autopsy is to be noted on the eCRF and a copy of the final autopsy is to be provided to St. Jude Medical. The primary objective of the autopsy is to determine the cause of death, complications and other relevant findings. In addition, special attention should be directed toward documentation of patient-prosthesis interaction and any HeartMate 3 LVAD associated complications.

19 DEVICE RETRIEVAL

Upon patient death or device explantation, all HeartMate 3 LVAS System Components (pump, system controller and modular cable/driveline) must be retrieved and returned to St. Jude Medical for analysis within 48 hours of explant. Devices must be returned using the Explant Kit and instructions.

20 PATIENT WITHDRAWAL

The patient retains the right to withdraw from the study at any time. Should the patient elect to withdraw from the study, the reason for withdrawal must be documented.

21 RISKS

The HeartMate 3 LVAS is a commercially available device in Kazakhstan and also the European Union (as of October 8, 2015 after receiving CE Mark approval).

The potential risks including anticipated adverse eventsare expected to be similar to those seen with other commercially available mechanical circulatory support devices.[1-4]

The patients enrolled in the HeartMate 3 CE Mark study that continue on HeartMate 3 support will be included in the CE Mark Long Term Follow-Up study. These patients will continue to be followed beyond the 2 years specified in the CE Mark study. No new patients will be exposed to risk and the patients in the study will not experience any new risk by being followed in the long term study.

22 MITIGATIONS

Mitigations and treatment for all adverse events should be per the current practice standards/standards of care as determined by the investigator. The long term follow-up care will continue with experienced and trained LVAS personnel.

23 BENEFITS

Commercially available mechanical circulatory support devices have been previously shown to provide safe and effective long term hemodynamic support in advanced heart failure patients with clinical meaningful improvement in survival, quality of life and functional capacity when compared to optimal medical management. It is therefore expected that similar benefits may be observed with the HeartMate 3 LVAS.

24 ETHICAL REQUIREMENTS

24.1 INFORMED CONSENT

Written informed consent must be obtained by the principal investigator or designee, before any study-related procedures or tests are performed that would otherwise not be performed according to the standard of care. If the patient is unable to participate in the informed consent process, consent must be obtained from a legally authorized representative prior to administering any study-related test or procedure. The use of a legally authorized representative is only permissible if allowed by the local EC.

If new information becomes available by the Sponsor that may affect a patient's participation in the trial, Investigators will be required to update/revise the informed consent as necessary, and all patients will be re-consented by the site.

Revisions to the informed consent will be approved by the Sponsor and the EC prior to re-consenting patients.

Each clinical site is responsible for keeping the original signed informed consent forms, and any updated signed informed consent forms for each patients on file, and available for inspection by St. Jude Medical.

The process of obtaining Informed consent must be documented in each patient's medical record.

24.2 VULNERABLE POPULATIONS

Vulnerable populations will not be recruited for this study.

24.3 ETHICS COMMITTEE REVIEW

Investigators will conduct the study in compliance with the Declaration of Helsinki[11] and local and national regulatory requirements.

St. Jude Medical will comply with all Ethics Committee and all national regulatory requirements.

Before initiation of the study, EC approval of the protocol and the informed consent form must be obtained. Modifications made to the ICF should be sent to St. Jude Medical for approval, prior to submitting to the EC. Copies of the EC submission and approval, including the approved informed consent form, must be forwarded to St. Jude Medical prior to the enrollment of patient into the study. A Final Report must be submitted by the investigator to the Ethics Committee and St. Jude Medical Corporation upon study termination or termination of site participation. Copies of all submissions to and correspondence from the Ethics Committee (approvals and disapprovals) must be sent to St. Jude Medical and maintained on file at the study site.

24.4 CONFIDENTIALITY

No individually identifiable/confidential patient data collected as part of this study will be released beyond St. Jude Medical. The patient will continue to be identified by the unique patient study identification code that was assigned during the CE Mark study. Patient identifiable data should be de-identified by the site prior to submission to St. Jude Medical.

25 PROTOCOL DEVIATIONS

This study should be conducted as described in this protocol. All deviations from the protocol will be flagged and evaluated through the Electronic Data Capture system (EDC).

For sites who demonstrate repeated deviations that may affect the safety of patients, and/or the integrity of the data, corrective measures will be instituted such as re-training.

Sites must notify their EC of protocol deviations in accordance with local EC requirements.

Refer to Section 29.5 for additional information on Sponsor management of Investigator compliance.

26 PROTOCOL AMENDMENTS

Significant changes to the protocol will be handled by a formal protocol amendment. Protocol amendments will be submitted to Investigators with instructions to submit their local ECs for approval.

27 DATA COLLECTION, CASE REPORT FORMS AND RECORD KEEPING REQUIREMENTS

27.1 DATABASE AND ELECTRONIC CASE REPORT FORMS (ECRFS)

An EDC system that complies with United States regulations on electronic records and signatures (21 CFR Part 11) will be utilized for this study. Users will have unique usernames and passwords, and the user list will be maintained by a St. Jude Medical administrator for all study personnel. The Investigator must ensure that the observations

and study findings are recorded correctly and completely in the eCRFs. Each eCRF requiring a signature must be signed and dated by the authorized personnel.

Data being submitted through the course of the clinical trial will be reviewed by the Sponsor for accuracy and completion. Database cleaning and the process for issuing and/or resolving queries will be documented in the Sponsors study specific data management plan.

27.2 DEVICE ACCOUNTABILITY RECORDS

The HeartMate 3 LVAS is not an investigational device in the European Union and Kazakhstan and therefore device accountability records will not be required. In Canada and Australia the HeartMate 3 LVAS has not yet received commercial approval and the devices will continue to be tracked via device accountability records.

Traceability of the LVAS is maintained by the Sponsor through the use of unique serial and/or lot numbers.

27.3 SOURCE DOCUMENTATION

Original Documentation supporting the data recorded on the eCRFs must be maintained, and include: clinical charts, medical records, laboratory reports, physician referral or consultation letters, X-ray reports, etc. Adverse events which are managed at a health care facility other than the study site must be reported on an eCRF and every attempt must be made to obtain source documentation from that facility.

Source documents may be be reviewed to ensure accuracy and validity of data recorded on the eCRFs. Source document verification will be performed by St. Jude Medical, or its designee, with due regard to patient confidentiality.

27.4 MAINTENANCE OF STUDY DOCUMENTATION

The following documents should be maintained by the study site, and copies of site specific documents sent to St. Jude Medical:

- Copy of the Study Protocol
- Ethics Committee Approval(s)
- Pertinent Ethics Committee Correspondence
- Ethics Committee approved Informed Consent Form(s), including translation certification if applicable
- Ethics Committee Membership Roster(s)
- Financial Disclosure(s)
- Investigator's Agreement(s)
- Curriculum Vitae(s)
- Study Staff Signature and Delegation of Responsibilities Log
- Laboratory Certification(s) and Normals
- Source documentation (such as patient clinic charts, medical records, laboratory records)
- Clinical Study Agreement (CSA)
- St. Jude Medical Correspondence
- Documentation of Training

- Monitoring Visit Log
- Instructions for Use (IFU)
- Patient Manual

27.5 RETENTION OF RECORDS

The investigator is responsible for retaining the necessary records in accordance with local country requirements. This includes a copy of the protocol, the device labeling, case report forms, medical records, original test result reports, all study-related correspondence, a record of written informed consent, and any other documents pertaining to the conduct of this study.

The investigator must not dispose of any records relevant to this study without either (1) written permission from St. Jude Medical or (2) providing an opportunity for St. Jude Medical to collect such records. The investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this study. Such documentation is patients to inspection by St. Jude Medical and regulatory bodies.

27.6 LABORATORY ACCREDITATION AND NORMAL VALUES

Only standard of care laboratory assessments will be collected during the study. Laboratories used should be accredited and the documentation provided to St. Jude Medical. Throughout the study, the Investigator should provide St. Jude Medical documentation of all renewals of accreditation.

28 INSURANCE

St. Jude Medical will obtain insurance to cover potential injury to patients in accordance with national requirements.

29 QUALITY CONTROL

29.1 INVESTIGATOR & SITE SELECTION

Prior to the initiation of the CE Mark study, investigators and sites were selected based on their qualifications and experience (qualified by education and training) to ensure patient safety and adherence to the protocol.

The Sponsor will maintain an updated list of principal investigators, investigation sites and/or institutions separately from the protocol. The list will be included in clinical investigation reports as required by EN ISO 14155:2011.

29.2 HOSPITAL STAFF TRAINING

Only trained personnel will perform study-related procedures. All clinical personnel (principal investigators, co-investigators, study coordinators) must be thoroughly familiar with the function, care and maintenance of the HeartMate 3 LVAS. These individuals underwent training by St. Jude Medical or designee prior to the CE Mark study initiation, and documentation of that training is maintained. The St. Jude Medical HeartMate 3 LVAS Instructions for Use will be provided to assist the healthcare team on the proper care and operation of the device.

29.3 MONITORING

St. Jude Medical is responsible for monitoring the study. St. Jude Medical or its designee will perform study monitoring remotely to ensure study progress and that the data is submitted in a timely manner. Ongoing communication with investigators and study staff will be performed through written correspondence and telephone conversations.

Details related to site monitoring will be documented in the Sponsor's study-specific monitoring plan.

The Investigator or designee upon request must provide to the sponsor the necessary study records for a thorough review of the study's progress. These records include, but are not limited to, case report forms and original source documents and records such as hospital and clinic charts, consent forms, and operative reports.

29.3.1 Study Close-out Activities

The following study close out activities will be performed prior to completion of the study:

- Ensure that all required eCRFs have been completed/submitted
- Remind the investigator of the obligation to retain the records in accordance with local country requirements, and prepare a final report for the sponsor and Ethics Committee.

29.4 INVESTIGATOR AND/OR STUDY SITE TERMINATION/SUSPENSION

If a serious compliance problem or deviation from the protocol is noted, St. Jude Medical will recommend corrective action

St. Jude Medical may consider terminating or suspending an investigator and/or study site in the following cases:

- Confirmed serious or repeated deviations and general non-compliance to the protocol
- Unacceptable critical changes in personnel, administrative, or scientific standards
- Unacceptable risk to patient safety is confirmed

In such cases, St. Jude Medical will notify the appropriate regulatory authority, and/or other participating centers as required by local and national regulations.

29.5 EARLY STUDY TERMINATION

St. Jude Medical reserves the right to discontinue the study. St. Jude Medical intends to exercise this right only for valid scientific or administrative reasons. After such a decision, all collected data must be entered into EDC.

30 EMERGENCY CONTACTS

Sponsor Contact:
Laura Damme, BSN, MPH
Director Clinical Studies, EMEA
St. Jude Medical
Burnett House
Ermine Business Park

Huntingdon, PE29 6UA, UK
Office phone: +44-1480-455200

All participating centers will be provided with country specific (Sponsor) emergency contact information for device related emergencies and/or safety reporting.

31 PUBLICATION POLICY

All publications will be reviewed by the study investigators and the Sponsor, and in accordance with the center specific Clinical Study Agreement (CSA).

32 HEARTMATE 3 CE MARK LONG TERM FOLLOW-UP STUDY VISIT SCHEDULE

	Enrollment	Month 36-60 (+/- 2 month)	As occurs
Inclusion/ Exclusion	X		
Enrollment	X		
EQ-5D-5L		X	
Modified Rankin Score[1]		X	X
NYHA Classification[2]		X	
Laboratory Assessments[3]		X	
Six Minute Walk Test		X	
Pump Parameters[4]		X	
Current Patient Status		X	
Patient Outcome			X
Rehospitalizations		X	X
Driveline Management		X	X
Pump Log Files[5]			X
Adverse Events		X	X
Device Malfunctions		X	X
Reoperations/Operative Procedures			X
Pump Replacements/ Exchanges			X
Autopsy[6]			X

[1] *Required only if a neurological event occurred.*
[2] *Must be performed by an independent assessor.*
[3] *Standard of Care laboratory assessments to be recorded*
[4] *Pump Parameters include: Pump Flow, Pump Speed, Pulsatility Index and Pump Power*
[5] *Pump Log Files include: Pump Period Log, Pump Event Log, Controller Period Log and Controller Event Log. These should be provided in cases of suspected device malfunction*
[6] *Required only if device related death occurred*

33 REFERENCES

1. Miller LW, Pagani FD, Russell SD, et al. Use of a continuous-flow device in patients awaiting heart transplantation. N Engl J Med 2007; 357: 885-896

2. Slaughter, MS, Rogers JG, Milano CA et al. Advanced Heart Failure Treated with Continuous-Flow Left Ventricular Assist Device N Engl J Med 2009; 361: 2241-2251

3. Starling RC, Naka Y, Boyle AJ et al. Results of the Post U.S. Food and Drug Administration-Approval Study with a Continuous Flow Left Ventricular Assist Device as a Bridge to Heart Transplantation, J Am Coll Cardiol 2011; 57:1890-1898.

4. Strueber, M. et al. Multicenter Evaluation of an Intrapericardial Left Ventricular Assist System .J Am Coll Cardiol. 2011; 57:1375-1382.

5. Active Implantable Medical Device Directive (AIMDD) 90/385/EEC. (June 20, 1990)

6. EN ISO 14155: 2011 - Clinical investigation of medical devices for human subjects – Part 1: General requirements

7. FDA. United States Code of Federal Regulations, Electronic Records: Electronic Signatures; Final Rule. Source: 21 CFR Part 11 (April 1, 2003).

8. GHT/SG5/N4: 2009 - Post Market Clinical Follow up Studies

9. Guidelines on Clinical Investigation: a Guide for Manufacturers and Notified Bodies, MEDDEV 2.7/4

10. Med Dev 2.12-2:2012 - Post Market Clinical Follow up Studies

11. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subject. 2013

12. Netuka I, Sood P, Pya Y, Zimpfer D, Krabatsch T, Garbade J, Rao V, Morshuis M, Marasco S, Beyersdorf F, Damme L, Schmitto JD. Fully Magnetically Levitated Left Ventricular Assist System for Treating Advanced HF: A Multicenter Study. J Am Coll Cardiol. 2015 Dec 15;66(23):2579-89.

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:
   - If transfusion is selected, then apply the following rules:

     During first 7 days Post-implant
     - 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
     - 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 MCSD 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., external pneumatic drive unit, electric power supply unit, batteries, controller, interconnect cable,)

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 patients 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 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 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 patient's health (e.g. cancer).

APPENDIX 2: 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. Patients 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. Patients 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. Patients 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 3: 6MWT PROTOCOL

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 patient 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 patient.
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 patient during the study.
5. A warm up prior to the test should not be performed.

Explaining the test procedure to the patient
1. Clearly explain to the patient 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 patient will re-state the instructions. If the patient does not seem to understand, repeat the entire instructions.

   Conducting the test
   1. Position the patient 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 patient takes the first step.
4. During the test, the walking pace of the patient should not be influenced. The test supervisor must walk behind the patient – do not walk with, rush up behind, or rush past the patient.
5. Each time the patient returns to the starting line, record the lap.
6. While walking, encourage the patient 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 patient should be spoken to only during the 1-minute encouragements; no response should be made to the patient's questions about the time and distance elapsed.
   a. If the patient is not concentrating on the walking, the patient can be reminded at a 1-minute mark:

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

9. 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 patient to STOP and walk over to him/her. Consider bringing a chair if the patient appears exhausted. Mark the spot where the patient stopped.

   If the patient wishes to stop walking during the test
   If the patient 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 patient 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 patient 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 patient sitting in a chair for at least 10 minutes after the test is completed.

APPENDIX 4: MODIFIED RANKIN SCORE

Score	Definition[1]
0	No observed neurological symptoms
1	No significant neurological disability despite symptoms; able to carry out all usual duties and activities
2	Slight neurological disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate neurological disability; requiring some help, but able to walk without assistance
4	Moderate severe neurological disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe neurological disability; bedridden, incontinent and requiring constant nursing care and attention as a result of a neurological deficit
6	Dead

[1] van Swieten J, Koudstaal P, Visser M, Schouten H, *et al* (1988). "Interobserver agreement for the assessment of handicap in stroke Subject". *Stroke* **19** (5): 604-607