A Prospective, Single Arm, Multi-Center Clinical Study in Collaboration with the InterAgency Registry for Mechanically Assisted Circulatory Support (INTERMACS®) to Evaluate the Thoracotomy Implant Technique of the HeartWare HVAD® System in Patients with Advanced Heart Failure

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Statistical Analysis Plan

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1. Introduction

1.1. List of Abbreviations

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BiVAD	Biventricular Assist Device
BMI	Body Mass Index
BSA	Body Surface Area (m^2)
BTT	Bridge to (Cardiac) Transplantation
CABG	Coronary artery bypass graft
CAP	Continuous Access Protocol
CCU	Coronary Care Unit
CI	Confidence Interval
CNS	Central Nervous System
CPB	Cardiopulmonary Bypass
CREB	Clinical Research Ethics Board
CT	Computed Tomography
CVA	Cerebral Vascular Accident (stroke)
DSMB	Data Safety Monitoring Board
Dy	Day / Days
ECMO	Extracorporeal Membrane Oxygenation
EuroQol (EQ)	European Quality of Life (EQ-5D)
GCP	Good Clinical Practice
GI	Gastrointestinal
HCVA	Hemorrhagic Cardiovascular Accident
ICF	Informed Consent Form
ICH	International Conference of Harmonization
ICU	Intensive Care Unit
ICVA	Ischemic Cardiovascular Accident
INTERMACS	InterAgency Registry for Mechanical Assisted Circulatory Support
IPD	Important Protocol Deviation
IRB	Institutional Review Board
ITT	Intent to Treat
KCCQ	Kansas City Cardiomyopathy Questionnaire (tool)
KM	Kaplan-Meier
LOS	Length of Stay
LV	Left Ventricle
LVAD	Left Ventricular Assist Device
MAP	Mean Arterial Pressure

Abbreviation	Definition
MRS (mRS)	Modified Rankin Scale
N or n	Number of Patients
NYHA	New York Heart Association (heart failure classification)
PMA	Pre-Market Approval
PP	Per Protocol
RVAD	Right Ventricular Assist Device
RVEF	Right Ventricular Ejection Fraction
SAS	Statistical Analysis System
SD	Standard Deviation
SE	Standard Error
TIA	Transient Ischemic Attack
UADE	Unanticipated Adverse Device Event
UCL	Upper Confidence Limit
VAD	Ventricular Assist Device
VAS	Visual Analog Scale
WHO	World Health Organization

1.2. Protocol Summary

This is a prospective, single arm, multicenter study to evaluate the safety and efficacy of the thoracotomy implant technique in 145 subjects implanted for the bridge to cardiac transplantation (BTT).

All subjects will be implanted via thoracotomy with the HeartWare Ventricular Assist Device (HVAD)® System and enrolled in the InterAgency Registry for Mechanically Assisted Circulatory Support (INTERMACS®) protocol and database.

This study will be conducted at up to 30 sites in the US and 1 site in Canada. All centers will be required to have an approved and active cardiac transplant program, have experience implanting the HeartWare® HVAD System, and must meet the INTERMACS® defined requirements to be eligible for participation.

One hundred forty-five (145) subjects will be required to meet the statistical endpoints defined for the study. It is anticipated that each site will enroll at least 1 subject. No site will implant more than 20 subjects into the study.

Subjects will be followed according to the INTERMACS® protocol and standard of care at the enrolling institution. Enrollment of subjects is expected to start in the fourth quarter of 2014 (First Implant) and each subject will be in the study for up to 60 months (including Screening and Follow-up phases).

The objective of this study is to evaluate the safety and effectiveness of implanting the HeartWare® HVAD System via thoracotomy in patients at risk of death from refractory end-stage left ventricular heart failure, who receive the device intended as a bridge to cardiac transplantation.

The primary endpoint is success at 6 months defined as all enrolled and implanted subjects:

- Alive on the originally implanted device at 6 months, and the subject has not had a stroke with a modified Rankin Scale ≥ 4 (assessed ≥3 months post stroke event); or
- Transplanted by Month 6, and the subject has not had a stroke with a modified Rankin Scale ≥ 4 (assessed ≥3 months post stroke event); or
- Explanted for recovery by Month 6, and the subject has not had a stroke with a modified Rankin Scale ≥ 4 (assessed ≥3 months post stroke event).

The secondary endpoint is an improvement in the mean length of initial hospital stay (initial recovery and step down unit) for all enrolled and implanted subjects. The mean length of initial hospital stay is estimated to be 26.1 days for median sternotomy subjects.

The Intent-to-Treat (ITT) subject population will include all enrolled subjects intended to receive the HVAD® pump via thoracotomy at the time of skin incision.

The Per-Protocol (PP) subject population will include all ITT subjects who were implanted with the HVAD pump® via thoracotomy, on-pump, and with outflow to the ascending aorta. Sample size requirements reflect the minimum number of subjects needed for the PP population.

Data recorded in the INTERMACS® database to the primary endpoint at 6 months post implant of the HeartWare® HVAD will be evaluated.

Subjects who remain on device support after the primary endpoint time-point, either the original device or exchange device, will be followed according to the INTERMACS® protocol until transplant, or until 5 years post implant of the original device. A subject's study participation is considered complete at either the time of induction of anesthesia for transplant, or at the 5 year post implant visit.

- Subjects who have been explanted for recovery prior to month 6 will be followed until their next scheduled follow-up visit according to the INTERMACS® protocol, at which time their participation in the study is considered complete.
- The per-protocol analysis population will include those thoracotomy subjects with the outflow in the ascending aorta only as well as those thoracotomy subjects with the procedure performed on-pump only. As a result, enrollment may exceed sample size requirements.

1.3. Study Objectives

The objective of this study is to evaluate the safety and effectiveness of implanting the HeartWare® HVAD System via thoracotomy in subjects at risk of death from refractory end-stage left ventricular heart failure, who receive the device intended as a bridge to cardiac transplantation (BTT).

2. Statistical Methods

2.1. Sample Size Estimate and Justification

2.1.1. Sample Size

Success at 6 months is estimated to be 86% compared to a performance goal of 77.5%. Using an exact binomial test, with a one-sided alpha of 0.05, and 80% Power, a sample size of 145 implanted subjects is required.

The target success estimate of 86% is based on the following:

- The primary endpoint observed in the final BTT IDE Report for the more recent BTT CAP population (N=242), resulted in a success rate of 85.8% (205 out of 239 eligible subjects) for sternotomy subjects.

- Post-approval data from the INTERMACS Registry (through Q2 2014), indicates similar results for the sternotomy population of 88.0% (396/450) with a lower rate of success for the small subset of thoracotomy (83.3%, 55/66) and thoracotomy on-pump (82.6%, 38/46) subjects.
- The INTERMACS Federal Partners Report (from Q1 2014) indicates an 85% Kaplan-Meier survival estimate at 6 months. This is not the same as "success" in that post-exchange survival is considered.

Success will be met if the lower bound of the upper one-sided exact 95% confidence interval is greater than 77.5%.

The mean length of initial hospital stay is estimated to be 26.1 days with a standard deviation of 22.8 days and a median of 20 days based on data from the BTT CAP population (N=242). Using a one sample t-test, with a one-sided alpha of 0.05, a sample of 145 implanted subjects with an average value of 21.3 days or less will result in power greater than 80%.

2.2. Patient Analysis Sets

There are two main analysis populations that will be used in results evaluation. These are the Intent-to-Treat (ITT) and Per-Protocol (PP) subject populations. All endpoints will be assessed on the ITT and PP populations.

2.2.1. Primary Analysis Set

The Per-Protocol (PP) subject population will include all ITT subjects who were implanted with the HVAD pump® via thoracotomy, on-pump, and with outflow to the ascending aorta and with no major protocol deviation.

2.2.2. Secondary Analysis Set

The Intent-to-Treat (ITT) population will include all enrolled subjects intended to receive the HVAD® pump via thoracotomy at the time of skin incision.

2.2.3. Selection of Control Patients

This is a single arm study wherein all subjects are implanted via thoracotomy with the HeartWare HVAD® System. No active control is used.

2.3. Interim Analysis

Section 11.5 of the protocol states that an interim analysis would be performed when the first 100 subjects completed 6 months of follow-up. No such analysis was performed. Since any change to the final alpha level would be considered negligible (0.001), there will be no effect on final endpoint analyses.

2.4. Analysis

The following section outlines the general statistical methods to be performed for efficacy and safety analysis.

No adjustments for multiplicity will be performed.

2.4.1. Primary Endpoint

The primary endpoint is success at 6 months for all enrolled and implanted subjects. Success is defined as follows:

- Alive on the originally implanted device at 6 months, and the subject has not had a severe stroke; or
- Transplanted by Month 6, and the subject has not had a severe stroke prior to transplant; or
- Explanted for recovery by Month 6, and the subject has not had a severe stroke prior to explant for recovery.

All subjects with stroke events from implant to Month 6 will be required to remain in study follow-up until the post-stroke mRS measure (≥3 months post stroke event) is obtained, even if this occurs at the next expected follow-up visit. If a stroke subject is alive at 6 months, but dies before the post-stroke mRS is obtained, the subject will be considered a failure with regard to the primary endpoint.

A stroke is considered severe if either:

- The first mRS score assessed ≥3 months post stroke event is ≥ 4; or

- The follow-up (≥3 months post stroke event) mRS score is missing and the day-of-event mRS is ≥ 4.

Specifically, any subject experiencing any of the following events will be considered a failure:

- Death by any cause prior to 183 days post-implant and prior to transplant or explant for recovery
- A severe stroke occurring prior to 183 days post-implant and prior to transplant or explant for recovery
- A stroke followed by death within 91 days post-event occurring prior to 183 days post-implant and prior to transplant or explant for recovery

Subjects with a stroke with no available mRS and no death ≥ 91 days post-stroke occurring prior to 183 days post-implant and prior to transplant or explant for recovery will be considered missing in the primary analysis.

All subjects with at least 182 days of documented follow-up without meeting any of the above failure criteria will be considered a success. Subjects not considered a success or a failure will be excluded from the analysis.

N.B. As INTERMACS only includes visits every 6 months starting at the 6 month visit, it should be noted that should a stroke occur after 3 months, a post-event mRS score may not be obtained until the 12 month visit.

Hypotheses:

H_0: $\pi_T \leq 77.5\%$

H_a: $\pi_T > 77.5\%$

where π_T = the proportion of the patient population experiencing success for the Thoracotomy group.

The success rate in this cohort will be statistically compared to the performance goal (77.5%) using an exact binomial test. Success will be met if the lower bound of the one-sided exact 95% confidence limit is greater than 77.5%.

2.4.2. Secondary Endpoint

The secondary endpoint is improvement in the length of initial hospital stay (initial recovery and step down unit) for all enrolled and implanted subjects, which is calculated by considering the number of days in acute care (ICU/CCU) plus the number of days in intermediate/step-down care (both variables taken as reported directly by INTERMACS), comprising the total number of days post-implant to discharge.

It is estimated that the mean length of initial hospital stay is 26.1 days for median sternotomy patients and thus the relevant hypotheses for this endpoint for each cohort are given by

H_0: $\mu_T \geq 26.1$

H_a: $\mu_T < 26.1$

where μ_T = the mean length of initial hospital stay for the Thoracotomy Implant Technique of the HVAD.

This secondary endpoint will be calculated and tested for each cohort using an upper tail one-sided t-test at 0.05 level of significance. Due to the skewed nature of this data, a one-sample sign test with an upper tail one-sided level of confidence of 0.05 will be conducted as supportive analysis.

The number and percentage of subjects with re-hospitalization after the initial hospitalization will be tabulated. Cumulative length of re-hospitalization after initial hospital stay (LOS) overall will be summarized using descriptive statistics, including 95% confidence intervals for the means.

2.4.3. Other Endpoints

Additional endpoints in this study include:

1. Success at 6 months defined as alive on original device or transplanted or explanted for recovery by month 6.

2. Overall Survival on HVAD (Time to Death on original device).

3. Frequency and rates of adverse events per INTERMACS® definition throughout original VAD support.
4. Time on Cardiac Pulmonary Bypass.
5. Perioperative Bleeding and Transfusions (within 48 hours post-op).
6. Length of initial ICU stay.
7. Prevalence and causes of re-hospitalizations (within 6 month period following implantation).
8. Health Status improvement at 6 month, as measured by KCCQ and EuroQol EQ-5D.
9. Functional status improvement, as measured by NYHA and 6-minute walk.
10. Success at 6 months (defined like the primary endpoint) for those screen failures who undergo thoracotomy.

Additional endpoints include observed and change in laboratory, hemodynamics and echocardiogram parameters and neurocognitive testing scores at 6 months. Additional observational endpoints will also be assessed at 6 months. The additional endpoints will be analyzed descriptively, i.e., no inferential analysis will be performed and conclusions will be formulated with caution as these endpoints are not powered.

Time-to-event outcomes will be presented using Kaplan-Meier curves. Quantitative outcomes will be summarized and the corresponding 95% confidence intervals will be derived. Categorical outcomes will be summarized by presenting frequency and percentage results as well as the corresponding 95% confidence intervals. In particular, adverse events and stroke events summaries will be presented by calculating prevalence (frequency) and event rates (events per patient-year).

Strokes are neurological events specified as an ICVA or an HCVA, as per the current INTERMACS event definition (See Appendix D of the protocol).

2.4.4. Demographics and Baseline Characteristics

Gender, race, and ethnicity will be summarized using counts and percentages. Age (years), height (cm), weight (kg), body surface area [BSA (m^2)], Body Mass Index (BMI) (kg/m^2) will be summarized with descriptive statistics.

The following baseline and pre-implant data recorded in the INTERMACS® database will be summarized:

- Patient demographic data.
- Medical history and co-morbidities.
- Clinical status including INTERMACS® patient profiles and NYHA Class.
- Laboratory values including blood chemistry and hematology.
- Cardiovascular Medications including inotropes, diuretics, anti-arrhythmics, pulmonary hypertensive agents, and anticoagulation therapy.
- Hemodynamic Data.
- Quality of Life as measured by EuroQol and KCCQ.
- Neurocognitive Testing measured by the Trail Making Neurocognitive Test, Part B.
- Exercise Function measured by the six minute walk test.

Continuous variables will be compared using the two-sided t-test, and the categorical variables will be compared using Fisher's Exact test. For the two sample t-test, the null hypothesis of equal variances among the groups will be checked. If the null hypothesis of equality of variance test is not rejected at the 0.05 level then the variances will be pooled, otherwise the Satterthwaite approximation for unequal variances will be used.

2.4.5. Patient Disposition

Disposition of Subjects

The number of subjects enrolled, who received an implant, and who are evaluable will be summarized. The number of treated subjects who completed the study, the number of subjects who discontinued from the study and the reasons for discontinuing from the study will also be summarized.

Protocol Deviations

Important protocol deviations (IPD) as defined by the HeartWare review team will be reported and presented with the final analysis.

2.4.6. Justification of Pooling

The primary and secondary endpoints will be performed on pooled data, however, an Analysis Site poolability assessment will be incorporated into the design of the study. This will involve pooling sites into "Analysis Sites" with a target size of 5 subjects. Sites with at least 5 subjects will serve at their own Analysis Site. Those with less than 5 will be rank ordered by size and sorted secondarily by site identification number to break ties. Starting with the smallest investigative site, subjects are combined site by site until at least 5 subjects are identified, thus establishing an Analysis Site. The next Analysis Site is formed similarly to contain at least 5 subjects. The process continues until all sites and subjects are accounted for. If the last Analysis Site has fewer than 5 subjects, it is combined with the most recently created previous Analysis Site.

A Fisher's exact test will be performed to test the homogeneity of success at 6 months across Analysis Sites. Analysis Site homogeneity is defined if the p-value is 0.15 or greater. If there is an Analysis Site effect (p-value < 0.15), an investigation of prognostic factors (i.e., baseline characteristics, medical history or other covariates of interest) will be reviewed to understand variability between Analysis Sites. As a supplemental analysis, a logistic regression model will be performed to estimate the probability of success controlling for Analysis Site and the selected prognostic factors.

2.4.7. Additional Analyses

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Adverse Events

i) Adverse Events based on INTERMACS definition

The number and percentage of subjects experiencing each specified AE using the INTERMACS definition will be summarized. Any AEs that are not treatment emergent will be listed only.

The incidence of AEs using the INTERMACS definition will be reported in the categories of bleeding (re-hospitalization, re-operation, gastrointestinal (GI)), cardiac arrhythmia (ventricular, supraventricular), device malfunction/failure, hemolysis, hepatic dysfunction, hypertension, infection (localized non-device, sepsis, driveline exit site), myocardial infarction, neurological dysfunction (CT confirmed ischemic cerebral vascular accident (CVA), CT confirmed hemorrhagic CVA , transient ischemic attack (TIA)), pericardial fluid collection, psychiatric

episode, renal dysfunction (acute, chronic), respiratory dysfunction, right heart failure (inotropic therapy, RVAD, inhaled nitric oxide), arterial non-CNS thromboembolism, venous thromboembolism, wound dehiscence, and other event. In addition to the incidence rate, the number of events and the event rate per patient year will be reported for each INTERMACS-defined adverse event. For the incidence rate, a subject will only be counted once per each INTERMACS-defined category and counted once per each INTERMACS-defined sub-category.

No statistical inference will be performed on adverse events.

2.5. Long-Term Follow-up Analyses

Adverse events through data cut will be included in the initial study results report. No other long term analysis will be included at that time. All data will be included in the final report.

2.5.1. Number and Timing of Proposed Analyses

Data collected post 6-months follow-up, i.e., 12, 18, and 24 months will be summarized and presented descriptively.

2.5.2. Endpoints

Analogue of the primary endpoint, as well as the secondary and other endpoints as possible will be included in post-6 months reporting.

2.6. Multivariate Analysis

No multivariate analysis is planned for this study.

2.7. References

1. Haybittle, J. L. (1971), “Repeated Assessment of Results in Clinical Trials of Cancer Treatment,” British Journal of Radiology, 44, 793–797.
2. Peto, R., Pike, M. C., Armitage, P., Breslow, N. E., Cox, D. R., Howard, S. V., Mantel, N., McPherson, K., Peto, J., and Smith, P. G. (1976), “Design and Analysis of Randomized Clinical Trials Requiring Prolonged Observation of Each Patient: I. Introduction and Design,” British Journal of Cancer, 34, 585–612.

3. Programming Considerations

3.1. Statistical Software

Version 9.4 or later of SAS® software will be the primary software used for statistical analysis.

3.2. Definition of Calculated Variables

1. Basic Variable Definitions

- Age will be calculated as the informed consent date minus the date of birth divided by 365.24 [Age=(ICF Date-DOB)/365.24]. Age will be rounded down to the nearest whole number
- Body mass index (BMI; kg/m^2) is calculated as: weight (kg) / [height (m)]^2, rounded to one decimal place.
- Body surface area (BSA; m^2) is calculated as:

  $BSA= (W*H/3600)^{0.5}$

  where W = weight in kg and H= height in cm
- Weights, heights, or temperatures recorded in alternate units will be converted to the units being displayed using standard conversion formulas.
- Length of Operative Time (Hours) = Time end of surgery for implantation – Time start of surgery for implantation
- Length of Initial Hospital Stay (Days) = Date of discharge following device implantation – date of hospitalization prior to device implantation + 1
- For days on or after the device is implanted:

Relative Study Day (Rel Day) = Date of Assessment – date of induction of anesthesia to implant of the study device + 1.

For days before the device is implanted:

Relative Study Day (Rel Day) = Date of Assessment – date of induction of anesthesia to implant of the study device.

- Days survived = Date of death/date of event for censoring – date of induction of anesthesia to implant of the study device + 1

- Days of hospitalization = Date of hospital discharge – Date of admission + 1
- Cumulative days of hospitalization after initial hospitalization is the sum of length of hospital stays after initial hospitalization.
- Days to first explant = Date of explant – date of induction of anesthesia to implant the initial study device + 1
- Days to first exchange = Date of exchange – date of induction of anesthesia to implant the initial study device + 1
- Days to transplant = Date of transplant – date of induction of anesthesia to implant the initial study device + 1
- Change from baseline (CFB) = Visit value – Screening/Pre-Implant value

2. Calculation of adverse event rate per patient-year

1. Calculate the patient-years contributed by each subject. The time in the study starts at enrollment. The end date would be the last follow-up date (end of study), unless the subject has an explant (when the pump is removed, turned off, or exchanged), dies, or is lost to follow-up prior to the end of study. The patient years are calculated as (date of explant or death or last follow-up or end of study – date of enrollment + 1)/365.24. When the number of days is negative, the value will be missing for the patient-years.

2. Sum the patient-years across all subjects in the study. This is the denominator.

3. Sum the total number of events for a particular adverse event (prior to exchange). If a subject has patient-years that is missing, the AEs will not be counted for these subjects (e.g., subjects who have ongoing AEs that are entered into the database, an exchange after the AE but prior to enrollment).

4. The adverse event rate per patient-year = (Sum of the total number of events for the particular adverse event (prior to exchange))/(Sum of the patient-years across all subjects in the study).