1 PROTOCOL/CIP NO. HW-PAS-03

**A Multi-Center, Post Approval Study
Providing Continued Evaluation and Follow-up on Patients
Who Received a HeartWare® Ventricular Assist System During IDE Trials
for the Treatment of Advanced Heart Failure**

Statistical Analysis Plan

**Prepared for:
HeartWare**

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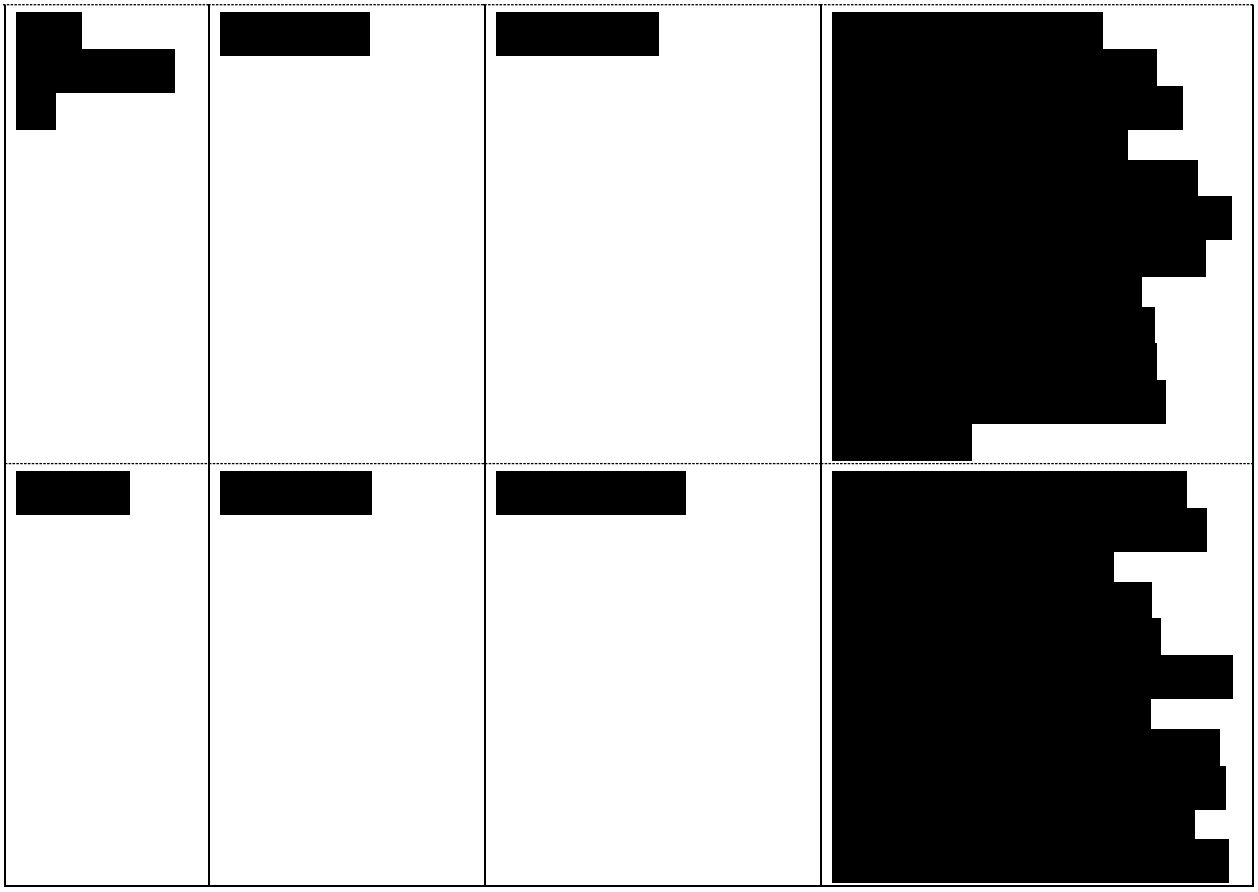

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In-Text Tables

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Descriptive Text
ADE(s)	adverse device effect(s)
AE(s)	adverse event (s)
AHA	American Heart Association
ATC	anatomical therapeutic chemical
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BSA	body surface area
BTT	Bridge to Transplant Trial
CAP	Continued Access Protocol
CFR	code of federal regulations
CI	confidence interval
CIP	Clinical investigation plan
cm	centimeters
CNS	central nervous system
CRF	case report form
CVA	cerebral vascular accident
DD	device deficiencies
EQ	EuroQOL
EU	European Union
FDA	Food and Drug Administration
g/dL	grams per deciliter
GCP	good clinical practice
HF	heart failure
HR	heart rate
hr(s)	hour(s)
HVAD	HeartWare ventricular assist device
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDE	Investigation device exemption
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
IPD	Important protocol deviations
IRB	institutional review board

Abbreviation	Descriptive Text
ITT	intent-to-treat
kg	kilograms
KCCQ	Kansas City Cardiomyopathy Questionnaire
KM	Kaplan-Meier
LOS	length of stay
LV	left ventricular
LVAD	left ventricular assist device
m	meters
max	maximum
MedDRA	Medical dictionary for regulatory activities
mg	milligram
MCID	meaningful clinical important difference (from baseline)
min	Minimum
mL	milliliters
ms	milliseconds
MRS	Modified Rankin Scale
N	number of patients
NIH	National Institutes of Health
NIHSS	National Institutes of Health Stroke Scale
NYHA	New York Heart Association
OS	Overall survival
OUS	Outside United States
PAS	Post approval study
PMA	Premarket Approval
QOL	Quality of Life
RHC	right heart catherization
RVAD	right ventricular assist device
SADE	serious adverse device effect
SAE	serious adverse event
SAP	Statistical analysis plan
SAS®	(statistical analysis software)
SD	standard deviation
SOC	system organ class
SOP	standard operating procedures
TEAE	treatment emergent adverse event
TEX	Time to Exchange

Abbreviation	Descriptive Text
TIA	transient ischemic attack
TRC	Time to Recovery
TTP	Time to Transplant
UADE	unanticipated adverse device effect
UNOS	United Network for Organ Sharing
US	United States
VAD	ventricular assist device
VAS	visual analogue scale
WHO	World Health Organization

3 INTRODUCTION

Heart Failure (HF) is a complex clinical syndrome caused by structural, metabolic and neurohormonal disorders that impair cardiovascular function, and is one of the leading causes of death in the developed world.

The worldwide prevalence of heart failure in adults is estimated to be 2-6%, with a higher prevalence in industrialized nations. Each year in the US, 670,000 new cases are identified and of the prevalent cases, 1 million are end-stage HF (NYHA class IV). There are approximately 5.7 million cases diagnosed in the United States and up to 14 million cases in the European Union. Advanced HF is associated with significant morbidity and disabling symptoms at rest. The one year mortality rate in patients newly diagnosed with NYHA class IV HF is approximately 25%. Improvements in treatment and survival as well as expansion of the aging population have contributed to the rising incidence and prevalence of the disease.

Cardiac transplantation is currently the most effective therapy for advanced heart failure. However, the lack of available donor organs restricts the use of heart transplantation to fewer than 2500 patients per year in the United States. In 2009, 2211 heart transplants were performed at 127 heart transplant centers in the United States (United Network for Organ Sharing website accessed December 15, 2011). Currently there are 3100 patients on the UNOS heart transplant list, with an average waiting time of approximately 6 months.

This Post Approval Study (PAS) is a study to provide continued and consistent follow-up on patients who have participated in prior IDE trials of HeartWare devices. Eligible patients include those who have reached the primary endpoint or outcome of that trial and entered longer term follow-up, as well as, those who have not yet achieved the primary endpoint or outcome at time of the PMA approval.

4 STUDY OBJECTIVES

The purpose of this multi-center, follow-up trial is to continue the evaluation of the safety and effectiveness of the HeartWare® Ventricular Assist System in patients who have been implanted with the HeartWare® Ventricular Assist System in the course of a prior HeartWare Trial under IDE G070199.

Endpoints that will be assessed include:

- Overall survival on device
- Final patient status
- Re-hospitalizations
- INTERMACS adverse events
- Quality of Life measures
- Functional Status

Safety measures will include the frequency and rates of adverse events, overall and for each specific event, which will be collected throughout HeartWare® Ventricular Assist System support.

[redacted]

5 STUDY DESIGN

5.1 General Design

A summary of the study design is presented here; complete details are provided in the protocol.

No new patients are being screened or implanted with the HeartWare® System for this trial; it is a follow-up trial only.

Patients will be approached to participate in this PAS after the HeartWare® Ventricular Assist System receives PMA approval for the indicated use as a bridge to cardiac transplantation.

Patients who participated in prior trials will be approached for this PAS as follows:

- Patients who are on continued HeartWare® System support, (original or exchange device)
- Patients who have been explanted for transplant or recovery and have not yet completed 6 months of follow-up

Patients who participated in prior trials who will not be approached to participate in this follow-up study include:

- Patients who have been explanted for transplant or recovery and have completed at least 6 months of follow-up (documented in the prior IDE trial).

All patients will have an enrollment visit and then be followed at 6 month intervals until 5 years post implant of the original HeartWare® device.

Patients who are explanted for transplant or recovery will be followed to 6 months post explant at which point their participation in the trial will be considered complete. This visit will record patient status only.

5.2 Discussion of Study Design

This is a post approval follow-up study based on two multicenter prospective, non- randomized, single-arm studies (BTT and CAP) to assess the clinical safety and performance of the LVAD pump for the treatment of advance heart failure. A multicenter study allows for scientific validity and generalization of the study findings. A follow-up of these studies allows for further monitoring of the safety and efficacy of the implanted device.

5.3 Method of Assignment of Patients to Treatment Groups

Not applicable as this is a follow-up study following previously implanted patients.

5.4 Blinding

Not applicable.

5.5 Determination of Sample Size

Not applicable as this is a follow-up study only and does not involve the screening and implant of new patients.

6 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

6.1 Changes in the Conduct of the Study

There were no changes in the conduct of the study at the time of preparing this statistical analysis plan.

6.2 Changes from the Analyses Planned in the Protocol/CIP

Section 6.1 and 6.3 were revised within this statistical analysis plan in order to remove references to medical history and add references to Patient Device Strategy. Medical history since termination of prior HeartWare Trial was previously included as one of the line items of the schedule of evaluations and enrollment visit. This was removed since this assessment will no longer be collected. In addition, Patient Device Strategy was added and will be collected at Enrollment visit and every 6 months for 5 years post implant.

7 BASELINE, EFFICACY AND SAFETY EVALUATIONS

7.1 Schedule of Evaluations

The assessments to be conducted at each scheduled visit are displayed in the following table.

Table 1 Time and Event Schedule

Event/Assessment	Enrollment	Every 6 Months for 5 Years Post Implant	Explanted or Transplant for Recovery 6 Months Post Explant	Explant from Previous IDE[1] 6 Months Post Explant
Visit Window	--	+/- 60 days	+/- 60 days	+/- 60 days
Informed Consent	X			X
Inclusion/Exclusion	X			
Demographics	X			
Patient Device Strategy	X	X		
Hemodynamic Parameters	X	X		
Safety Laboratory Chemistry	X	X		
Safety Laboratory Hematology	X	X		
LVAD Parameters	X	X		
Exercise Function - 6-Minute Walk	X	X		
NIH Stroke Scale / Modified Rankin Scale *	X	X		
NYHA Classification	X	X		
Patient Status	X	X	X	X
Kansas City Cardiomyopathy Questionnaire (KCCQ)	X	X		
Quality of Life Questionnaire (EuroQol EQ-5D-5L)	X	X		
Neurocognitive Testing	X	X		
Medications	X	X		
Adverse Events	X	X		

* NIH Stroke Scale (NIHSS) and MRS assessments is gathered at enrollment into this study, at the next scheduled assessment relative to implant, and every 6 months thereafter while on device. NIHSS and MRS assessment is required in the event of a neurological event.

1 – Patient has not yet completed 6 months post follow up visit.

7.2 Time Point Algorithms

7.2.1 Relative Day

The date the device is implanted will be considered relative day 1, and the day before the device is implanted will be relative day -1. Relative days will be calculated as follows only when the full assessment date is known (i.e., partial dates will have missing relative days):

For days on or after the device is implanted:
Relative Study Day (Rel Day) = Date of Assessment – Date of implant + 1.

For days before the device is implanted:
Relative Study Day (Rel Day) = Date of Assessment – Date of implant.

7.2.2 Windows

For the purpose of statistical analysis, analysis visits will use nominal visit designation based on time since device implant.

If a patient has more than one assessment occurring in the same visit window, the data from the visit closest to the scheduled study day will be used. If two visits have the same distance from the scheduled study day, the data from the visit after the scheduled study day will be used.

7.3 Enrollment Visit Assessments

The following procedures will be performed at the Enrollment Visit for all patients active on device:

- Date of Assessment
- Obtain signed and dated written ICF
- Inclusion/Exclusion
- Record Demographics
- Record Patient Device Strategy
- Measure Hemodynamic parameters
- Collect blood samples for laboratory testing
- Record LVAD Parameters

- Perform NYHA Classification
- Perform 6- Minute Walk Test
- Record patient status
- NIH Stroke Scale/Modified Rankin Scale
- Collect Neurocognitive function data
- Collect Kansas City Cardiomyopathy Questionnaire
- Collect Quality of life questionnaire (EuroQol EQ-5D-5L)
- Record concomitant medication taken by the patient
- Document adverse events reported from date of signature of the ICF including ongoing adverse events from the premarket trial

For patients who have been explanted for transplant or recovery in the prior IDE trial, and have not completed 6 months post explant follow up:

- Date of Assessment
- Obtain signed and dated written ICF
- Record patient status

Additionally the patient identifier from the prior trial and the trial ID will be captured.

Time from implantation to enrollment into HW-PAS-03 will also be calculated as:
Time from implantation to enrollment into HW-PAS-03 = date of enrollment – date of implant + 1.

7.4 Observational Efficacy Variables

7.4.1 Overall Survival at 60 months

Overall Survival (OS) is defined as the time from date of implant until date of death on device (in days). If a patient had a transplant, or myocardial/ventricular recovery, OS will be censored at the time of this event date. For each patient that remains alive on device, OS will be censored at the time of last contact date known to be alive (contacts considered in the determination of last contact date would include but not limited to scheduled visit dates, adverse event date, and last known alive date).

Overall Survival = Date of event/censor – Date of Implant + 1.

[redacted]

7.4.3 Final Patient Status

Patient Status will be gathered at enrollment into this study, at the next scheduled assessment relative to implant, and every 6 months thereafter while on device. If the patient has device removed or turned off, the patient status will be gathered 6 months post event. The final patient status will be determined after the patient has completed the 60 months post-implant follow-up or has terminated the study early.

7.4.4 Health Status, as measured by EuroQol EQ-5D-5L

The EuroQol-5-dimension 5-level (EQ-5D-5L) questionnaire is a measure of health-related quality of life that quantifies five domains of well being (Herdman, et. al., 2011). The 5 dimensions of health status are

- Mobility (MO)
- Self-care (SC)
- Usual activities (UA)
- Pain and discomfort (PD)
- Anxiety and depression (AD)

EuroQol-5D-5L assessments will be gathered at enrollment into this study, at the next scheduled assessment relative to implant, and every 6 months thereafter while on device.

Two summary values will be provided from the EQ-5D-5L, EQ-VAS and EQ index value. The EQ VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labeled 'the best health you can image' (score=100) and 'the worst health you can imagine' (score =0). The EQ index value is determined using the excel file calculator available at EuroQOL website (http:// euroqol.org/about-eq-5d/valuation-of-eq-5d/eq-5d-5l-value-sets.html) that is based on validation studies from Van Hout, et.al. (2012). From the EuroQoL-5D-5L value sets, the U.S. appropriate norms will be used. Further details of the EQ-5D-5L determination is presented in the Appendix.

All EQ-5D-5L data will be sent to a core laboratory, The Methodist Hospital Neurological Institute in Houston, Texas. The index value will be calculated by the core laboratory and then provided to HeartWare using Neurocognitive Testing Score form.

7.4.5 Health Status, as measured by Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KCCQ is a self-administered instrument that quantifies physical limitation, symptoms (stability, frequency, and burden), social limitation, self-efficacy and quality of life. KCCQ assessments will be gathered at enrollment into this study, at the next scheduled assessment relative to implant, and every 6 months thereafter while on device.

The KCCQ is composed of 15 questions. The questions are grouped to reflect clinically relevant domains: physical limitation (question 1a-1f), symptom stability (question 2), symptom frequency (questions 3, 5, 7, 9), symptom burden (questions 4, 6, 8), self-efficacy (questions 10, 11), quality of life (questions 12, 13, 14), and social limitation (question 15a-15d). To facilitate interpretability, three summary scores were developed, overall summary score, total symptom score, and clinical summary score. Further details of the KCCQ determination are presented in the Appendix.

Scale scores for the summary scores (overall summary, clinical summary, total symptom) and for each domain (physical limitation, symptom (frequency, stability, burden), self-efficacy, social limitation, quality of life) will be calculated for each patient at each time point.

7.4.6 Functional status, as measured by NYHA

The number of patients by NYHA Class will be determined at each time point. The denominator will be the number of patients on the device at the given time point and completed the assessment form.

7.4.7 Functional status, as measured by 6-minute walk

The distance walked in meters in 6 minutes will be reported at each time point. Missing data in patients who did not perform the 6-minute walk due to early termination will not be imputed. Those patients will be excluded from the analysis. Missing data in patients who were medically unable to or indicated that they could not perform the 6-minute walk task (for any reason) will be imputed to zero (0). If a patient missed a visit or the associated CRF page was not filled out at a visit then no imputation will be done.

7.4.8 NIH Stroke Scale

NIH Stroke Scale (NIHSS) assessments will be gathered at enrollment into this study, at the next scheduled assessment relative to implant, and every 6 months thereafter while on device. NIH Stroke Scale (NIHSS) assessment will be required in the event of a neurological event. The total raw NIHSS score will be used for reporting purposes.

7.4.9 Modified Rankin Scale

The Modified Rankin Scale (MRS) will be gathered at enrollment into this study, at the next scheduled assessment relative to implant, and every 6 months thereafter while on device. MRS will be required in the event of a neurological event.

7.4.10 Neurocognitive Testing

Neurocognitive function data will be measured by the Trail Making Neurocognitive Test, Part B at enrollment and every 6 months until year 5 post-implant or study discontinuation (whichever comes first). This test of general cognitive function also specifically assesses working memory, visual processing, visuospatial skills, selective and divided attention and psychomotor coordination for the Neurocognitive Function Test.

All neurocognitive test data will be sent to a core laboratory, The Methodist Hospital Neurological Institute in Houston, Texas. Data will be interpreted following standard conventions and using standard published norms for each test. Raw and z-scores will be calculated by the core laboratory and then provided to HeartWare using Neurocognitive Testing Score form.

7.5 Drug Concentration Measurements and Pharmacokinetic Parameters

Not applicable to this study.

7.6 Safety Variables

7.6.1 Extent of Exposure and Compliance to Study Treatment

This is a post approval study; all qualified patients have been previously implanted with the investigational device in the hospital.

Duration on original device, duration on device, and duration in study since original implant will be calculated for each patient.

Duration on original device (days) = date of first explant/transplant/exchange – date of implant + 1

Duration on device (days) = date of first explant/transplant – date of implant + 1

Duration in study since original impant (days) = date the patient discontinued/completed from the study – date of implant +1

For patient discontinued or completed the study with the original device, the duration on original device/device will be the same as duration on study.

7.6.2 Adverse Events

The investigator's verbatim term for all adverse events (AEs) will be mapped to system organ class (SOC) and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA).

An AE in this study is any untoward medical occurrence, unintended disease or treatment injury, or any untoward clinical signs (including an abnormal clinical laboratory finding). This includes events related and unrelated to the investigational medical device or the procedures involved. An AE will be considered emergent if the onset of the event is on or after the start of enrollment into this study. For the purposes of summary reporting of AEs, AEs will be reported while on original device.

In addition, INTERMACS-defined AEs occurring during the study will be recorded. The definition for all INTERMACS-defined AEs can be found in Appendix 20.8 of the protocol. The category of other adverse events will be those adverse events that were unable to be reported into an INTERMACS-defined adverse event category. For the INTERMACS-defined adverse events, the number of events per person-year will be calculated.

For each event, the potential etiology of the event will be determined by the investigator and categorized as:

1. Related to Procedure
2. Related to LVAD System
3. Undetermined
4. Patient Condition
5. Other

Any event categorized as related to or possibly related to the procedure or LVAD system will be considered an adverse device event (ADE). Any event only categorized as related to or possibly related to patient condition, undetermined or other will be considered a non adverse device event (non ADE).

For an event where the relationship is missing, the relationship will be considered related for analysis purposes.

7.6.2.1 Non Adverse Device Event (non ADE)

Adverse events not related to the use of the investigational medical device. This includes events reported due to the patient condition or not able to be determined to be related to the medical device. A non adverse device event (non ADE) will be considered emergent if the onset of the event is on or after the start of the implant surgery.

7.6.2.2 Device or Procedure Related

Adverse Device Event (ADE)

Adverse events related to or possibly related to the use of the investigational medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunctions of

the investigational medical device or as a result of a user error or intentional misuse. All ADEs are considered emergent.

Unanticipated/Unexpected Adverse Device Event (UADE)

An UADE is an event which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. The anticipated/expected adverse events are defined in Section 11.6 of the protocol. All UADE are considered emergent.

7.6.2.3 Serious Adverse Event

A serious adverse event (SAE) is an AE that led to death, led to serious deterioration in health that resulted in life-threatening illness or injury, in permanent impairment of a body structure or body function, in the patient's hospitalization or prolongation of existing hospitalization, in medical or surgical interventions to prevent life threatening illness, or in a injury or permanent impairment to a body structure or a body function, led to fetal distress, fetal death or a congenital abnormality or birth defect.

A serious adverse device effect (SADE) is an event that resulted in any of the consequences characteristic of a serious adverse event.

7.6.3 Clinical Laboratory Evaluations

Clinical laboratory tests are scheduled at enrollment into this study, at the next scheduled assessment relative to implant, and every 6 months thereafter while on device. All clinical laboratory test results will be reported in or converted to Standard SI units for analysis. Clinical laboratory results will also be classified as normal (if value is within normal reference range) or abnormal (if value is either below (L) or above the normal reference range (H)).

7.6.4 Other Safety Variables

7.6.4.1 Hemodynamic Parameters

Hemodynamic parameters are scheduled at enrollment into this study, at the next scheduled assessment relative to implant, and every 6 months thereafter while on device. The hemodynamic parameters include systolic and diastolic blood pressure, heart rate, mean arterial

pressure and cardiac output. Some parameters are available only during right heart catherization (RHC) monitoring, while others are not available due to RHC monitoring. In addition, some parameters may not be available in some patients who have a VAD implanted.

7.6.4.2 Re-hospitalization

Information on re-hospitalizations post enrollment will be collected. This includes date and reason for re-admission to hospital, date of discharge, procedures performed and other diagnostics test results. Length of stay will be determined.

Length of stay = date of discharge – date of hospitalization + 1.

7.6.4.3 Explant

The number of patients with an explant of the device will be tallied. The denominator will be the number of patients with a device implanted. Also the time to explantation of the device will be the number of days from when the explant occurred after the device implantation.

Time to Explant in days = date of explant – date of implantation + 1

The reason for explant will also be recorded.

8 STATISTICAL METHODS

8.1 General Methodology

All statistical tests will be two-sided with a significance level of α=0.05, unless specified otherwise, and will be performed using SAS® Version 9.2 or higher. Data will be summarized using descriptive statistics (number of patients [N], mean, standard deviation [SD], median, minimum, and maximum) for continuous variables and using frequency and percentage for discrete variables. [redacted]

[redacted]

Patient listings of all data from the case report forms (CRFs) as well as any derived variables will be presented.

8.2 Adjustments for Covariates

No covariates are planned to be used in the analyses for this study.

8.3 Handling of Dropouts or Missing Data

Patient-years and follow-up time are based on database-driven known time on LVAD support (including post-exchange time). If a patient is on LVAD support at last known follow-up and a later date of death exists, the date of death must be considered the last follow-up for that patient. The patient is known to be alive and assumed to be on LVAD support up to the date of death.

If a partial date is reported where the day is missing, then the day will be imputed as the first day of the month unless the month is the same month as the device is implanted then then the day will be that of implantation with the month and year remaining the same. If a partial date is reported where the month is missing, then the month will be imputed to January unless the year is the same year as the device is implanted then the month will be that of implantation with the year remaining the same. If a partial date where both the day and month is missing, follow details as stated previously.

Missing data for other parameters will not be imputed for analysis unless defined in Section 6. Censoring for the efficacy endpoints is discussed in Sections 6.4.1. Missing adverse event dates will be imputed using partial date imputation rules as previously described in this Section.

8.4 Interim Analyses and Data Monitoring

Interim reports will be submitted at 6-months, 12 months, 18 and 24 months then if applicable, yearly until the end of study follow-up. The report after the last patient has completed the 5 year (60 month) follow-up visit post original device implant will be the end of study, or final report.

8.5 Multi-center Studies and Pooling of Centers

No pooling of centers within a study will be performed.

8.6 Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons or multiplicity will be performed.

8.7 Use of an "Efficacy Subset" of Patients

Not applicable to this study.

8.8 Active-Control Studies Intended to Show Equivalence

Not applicable to this study.

[redacted]

9 STATISTICAL ANALYSIS

9.1 Disposition of Patients

The number of patients enrolled, who received an implant, and who are evaluable will be summarized [redacted] The time in days post implant when entering enrollment of this follow-up will also be summarized. Patients who are exchanged to another FDA approved VAD, explanted for transplant, or recovery will be followed to 6 months post explant at which point their participation in the trial will be considered complete. The visit summary based on the 6 month post-implant interval will be presented as well as descriptive statistics.

A listing showing all patients' status and disposition by time point will be presented. A listing of study termination reasons will also be displayed.

9.2 Protocol Deviations

Protocol Deviations will be entered into the database and will be summarized by HeartWare Project Manager or Lead CRA. The review of protocol deviations will be completed just prior to database closure for the interim analysis and database lock for final analysis. Once all protocol deviation determinations are finalized and approved by the HeartWare review team, the database will be closed for statistical analysis.

The protocol deviations will be classified as one of the following:

1. Informed Consent
2. Inclusion/Exclusion Criteria Not Met
3. Non-Compliance with Visit Schedule
4. Partial Assessment Not Done
5. Full Assessment Not Done
6. Required Assessment Not Done in Required Timeframe
7. Procedure
8. Other

9.3 Analysis Populations

9.3.1 Enrolled Population

All patients who signed informed consent will be included in this analysis set. This analysis set will be used only for patient accountability for disposition purposes.

9.3.2 Intent-to-Treat (ITT) Population

All patients who enroll to the study (i.e., have signed informed consent) and who were at risk of death from refractory, advanced heart failure and implanted with a HeartWare Ventricular Assist System under IDE G070199 will be included in this analysis set. This is the full analysis set. This population will be used for patient disposition reporting purposes and for overall survival analysis.

9.3.3 Intent-to-Treat On Device Population

All patients in the ITT population who have the primary HeartWare Ventricular Assist System implanted at the time of enrollment or had an exchange for another HeartWare device will be included in this analysis set. This population will be used for all summaries. as well as disposition tables and overall survival analysis (both populations will be analyzed).

9.3.4 Safety Population

Patients in the ITT on device population will form the Safety Population.

9.4 Demographic and Other Characteristics at Enrollment

Demographic and other characteristics at enrollment will be summarized for the ITT on device population. [redacted]

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

General hemodynamic parameters (systolic and diastolic blood pressure, heart rate, cardiac output, and mean arterial pressure) collected at enrollment will be summarized with descriptive statistics.

The time from implantation will be summarized using descriptive statistics. These measurements will also be summarized by 6 month post-implant intervals by counts and percentages.

Listings of demographic information and other characteristics will be displayed.

9.5 LVAD Parameters

LVAD parameters, including flow, speed, and power, will be tabulated by time point with descriptive statistics. Suction detection and alarms will also be recorded. This summary will be performed for ITT on device population. A listing of LVAD pump parameters will also be displayed.

9.6 Concomitant Therapy

The World Health Organization (WHO) Drug Dictionary will be used to classify medications by preferred term and WHO Anatomical Therapeutic Chemical (ATC) classification of ingredients.

Medications will be summarized using counts and percentages by WHO ATC classification of ingredients and by preferred term. This summary will be performed for ITT on device population. A listing of all concomitant medications will be displayed.

9.7 Analysis of Protocol-Defined Efficacy Parameters

All protocol-defined efficacy analyses will be performed on either the ITT or the ITT on device populations, or both. [redacted]

9.7.1 Overall Survival at 60 Months

Overall survival (OS) rates will be derived from the Kaplan-Meier estimates. The quartiles of survival time will be presented along with 95% confidence intervals. A log-rank (two-sided) test

[redacted] This analysis will be performed on the ITT population as well as the ITT on device population. A listing of overall survival for each patient will be displayed.

[redacted]

9.7.3 Kansas City Cardiomyopathy Questionnaire (KCCQ)

KCCQ scale scores will be summarized by visit using descriptive statistics, including 95% CI for the mean. Only patients that are currently on device at the given time point will be summarized. This analysis will be performed on the ITT on device population. A listing of KCCQ data will be displayed for each domain.

The KCCQ scores for Physical Limitation, Symptom Stability, Social Limitation, Self-Efficacy, Quality of Life, Clinical Summary Score and Overall Summary Score will be summarized by visit from baseline (i.e., including data from the original IDE trials) for the ITT on device population. Descriptive statistics will be used and a comparison from baseline will be shown, including a 95% CI about the mean change from baseline.

9.7.4 EuroQol-5D-5L

EQ-5D-5L health profiles will be tabulated by time point and level of perceived problems (1=no problem; 2=slight problem; 3=moderate problems; 4=severe problems; 5=extreme problems) using counts and percentages. EQ VAS data will be tabulated by time point using descriptive statistics, including the 95% CI for the mean. The EQ index value will be tabulated by time point using descriptive statistics of sample size (N), mean, 95% CI for the mean, minimum, maximum, median, and standard deviations. Only patients that are currently on device at the given time point will be summarized. This analysis will be performed on the ITT on device population. A listing of the quality of life questionnaire data will also be displayed.

9.7.5 6-Minute Walk

Results of the 6-minute walk at each visit will be tabulated by time point using descriptive statistics, including 95% confidence intervals for the means. This analysis will be performed on the ITT on device population. A listing of all 6-minute walk test data will be presented.

The 6-minute walk results will be summarized by visit from baseline (i.e., including data from the original IDE trials) for the ITT on device population. Descriptive statistics will be used and a comparison from baseline will be shown, including a 95% CI about the mean change from baseline.

9.7.6 NYHA Classification

Results of the NYHA classification collected during the study will be tabulated by time point using counts and percentages. This analysis will be performed on the ITT on device population. A listing of all NYHA classification data will also be presented.

The NYHA classification results will be summarized by visit from baseline (i.e., including data from the original IDE trials) for the ITT on device population using counts and percentages.

9.7.7 NIH Stroke Scale

Results of the NIHSS collected during the study will be tabulated by time point using descriptive statistics, including 95% confidence intervals for the means. This analysis will be performed on the ITT on device population. A listing of all NIHSS data will be displayed as well.

9.7.8 Modified Rankin Scale

Results of the MRS by category will be tabulated by time point using counts and percentages. This analysis will be performed on the ITT on device population. A listing of all MRS data will also be presented.

[redacted]

[redacted]

[redacted]

9.8 Analysis of Safety

All safety analyses will be performed using the safety population. [redacted] Formal inferential statistics will not be conducted.

9.8.1 Extent of Exposure and Compliance to Study Treatment

Duration on original device, duration on device and duration in study since the original implant will be summarized for both ITT and ITT on device populations.

9.8.2 Adverse Events

9.8.2.1 Adverse Events based on INTERMACS definition

The number and percentage of patients experiencing each specified AE using the INTERMACS definition will be summarized. Each AE summary will also be presented for AEs occurring on original device and post-exchange to another HeartWare device. Any AEs that are not treatment emergent or occurred after the removal of the original device (without exchange to another HeartWare device) 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 patient will only be counted once per each INTERMACS-defined category and counted once per each INTERMACS-defined sub-category. The following summaries will be presented.

1. All Treatment Emergent AEs by INTERMACS-defined term
[redacted]
4. All Treatment-Emergent AEs by INTERMACS-defined term for HeartWare Devices
[redacted]
7. All Treatment Emergent ADEs by INTERMACS-defined term
8. All Treatment Emergent ADEs by INTERMACS-defined term for HeartWare Devices
9. All Treatment Emergent Non-ADEs by INTERMACS-defined term
10. All Treatment Emergent Non-ADEs by INTERMACS-defined term for HeartWare Devices
11. All Treatment Emergent ADEs by INTERMACS-defined term – Related to LVAD System
12. All Treatment Emergent ADEs by INTERMACS-defined term – Related to LVAD System for HeartWare Devices
13. All Serious AEs by INTERMACS-defined term
14. All Serious AEs by INTERACS-defined term for HeartWare Devices
15. All Serious ADEs by INTERMACS-defined term
16. All Serious ADEs by INTERMACS-defined term for HeartWare Devices
17. All Serious non-ADEs by INTERMACS-defined term

18. All Serious non-ADEs by INTERMACS-defined term for HeartWare Devices
19. All Serious ADEs by INTERMACS-defined term – Related to LVAD System
20. All Serious ADEs by INTERMACS-defined – Related to LVAD System for HeartWare Devices
21. All Treatment Emergent AEs leading to outcome of fatal by INTERMACS-defined term
22. All Treatment Emergent AEs leading to outcome of fatal by INTERMACS-defined term for HeartWare Devices
23. All Treatment Emergent AEs leading to exchange/explant of device by INTERMACS-defined term
24. All Treatment Emergent AEs leading to exchange/explant of device by INTERMACS-defined term for HeartWare Devices

A listing of deaths, including the INTERMACS category (and verbatim term, if applicable), adverse event number and narrative will be provided.

In addition, an adverse event table, for the ITT on device population, will be created to include events on original device and post-exchange (including post-exchange follow up time) from the date of original implant (i.e., including events from the original IDE trials).

A listing of all device malfunction/failure events (original device and post-exchange) from the date of original implant (i.e., including events from the original IDE trials), will be provided.

9.8.2.2 Adverse Events Categorized as Other in the INTERMAC definition based on MedDRA

All adverse events (AE) that were categorized as 'Other' in the INTERMACS definition will be summarized by system organ class (SOC) and preferred term; events that are not treatment emergent or occurred after the removal of the original device (without exchange to another HeartWare device) will be listed only. A patient will only be counted once per system organ class and once per preferred term within a system organ class. Patient counts and percentages and event counts as well as event rate per patient year will be presented in the following summaries.

1. All Other Treatment Emergent AEs by SOC and preferred term [redacted]

[redacted]

4. All Other Treatment Emergent AEs by SOC and preferred term for HeartWare Devices

[redacted]

7. All Other Treatment Emergent ADEs by SOC and preferred term
8. All Other Treatment Emergent ADEs by SOC and preferred term for HeartWare Devices
9. All Other Treatment Emergent Non-ADEs by SOC and preferred term
10. All Other Treatment Emergent Non-ADEs by SOC and preferred term for HeartWare Devices
11. All Other Treatment Emergent ADEs by SOC and preferred term – Related to LVAD System
12. All Other Treatment Emergent ADEs by SOC and preferred term – Related to LVAD System for HeartWare Devices
13. All Serious Other AEs by SOC and preferred term
14. All Serious Other AEs by SOC and preferred term for HeartWare Devices
15. All Serious Other ADEs by SOC and preferred term
16. All Serious Other ADEs by SOC and preferred term for HeartWare Devices
17. All Serious Other non-ADEs by SOC and preferred term
18. All Serious Other Non-ADEs by SOC and preferred term for HeartWare Devices
19. All Serious Other ADEs by SOC and preferred term – Related to LVAD System
20. All Serious Other ADEs by SOC and preferred term – Related to LVAD System for HeartWare Devices
21. All Other Treatment Emergent AEs leading to outcome of fatal by SOC and preferred term
22. All Other Treatment Emergent AEs leading to outcome of fatal by SOC and preferred term for HeartWare Devices
23. All Other Treatment Emergent AEs leading to exchange/explant of device by SOC and preferred term
24. All Other Treatment Emergent AEs leading to exchange/explant of device by SOC and preferred term for HeartWare Devices

Adverse events potentially related to study device are defined as a subset of adverse events with a relationship to study device of either possible related or related. Events with missing relationship assessment will be included as potentially related to study device.

No statistical inference will be performed on adverse events.

Listings will be presented by patient for all adverse events as well as for each INTERMACS definition, UADEs, SAEs, adverse events associated with death, and adverse events leading to study device explant/exchange.

9.8.3 Clinical Laboratory Evaluations

Clinical laboratory test values at each visit will be summarized using descriptive statistics. All clinical laboratory data will be presented in listings. Within each listing, laboratory values outside the normal ranges will be flagged as either high (H) or low (L).

9.8.4 Other Variables Related to Safety

9.8.4.1 Hemodynamic Parameters

Hemodynamic parameters at each visit will be tabulated with descriptive statistics by time point. A listing of all hemodynamic parameters will be also presented.

9.8.4.2 Re-hospitalization

The number and percentage of patients with re-hospitalization after enrollment will be tabulated by category of stay: 1, 2, 3 or greater. The number of re-hospitalizations will also be summarized using descriptive statisics. Reason for hospitalization and procedures performed will also be tabulated using counts and percentages. Length of stay will be summarized by counts and percentages for each of the following categories: <= 7 days, 8-14 days, and > 14 days. Overall length of stay will also be summarized using descriptive statistics (sample size (N), mean and 95% confidence intervals for the means, minimum, maximum, median, and standard deviation).

A listing showing all patients hospitalizations will be displayed.

9.8.4.3 Explant

Number and percentage of patients with an explantation will be tabulated. Time to first explantation relative to initial implant will be assessed using descriptive statistics (sample size (N), mean and 95% confidence intervals for the means, minimum, maximum, median, and standard deviation). Also the time to first explantation relative to initial implant in the following categories:

- Explant occurred $\leq$ 30 days after implant
- Explant occurred $\leq$ 180 days after implant
- Explant occurred $>$ 180 days after implant

The time to first explantation is only calculated for explants that occur on study.

Number and percentage for reasons for explantation will be tabulated. Since patients can have multiple explants, the reasons for explantation will include all reasons. Therefore the percentages may add up to more than 100%.

10 COMPUTER SOFTWARE

All analyses will be performed by Chiltern International (formerly Theorem Clinical Research) using Version 9.2 or later of SAS® software. All summary tables and data listings will be prepared utilizing SAS® software.

The standard operating procedures (SOPs) of Theorem Clinical Research will be followed in the creation and quality control of all data displays and analyses.

11 APPENDICES

11.1 APPENDIX 1: 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 using Mosteller formula as:
  $BSA= (H * W / 3600)^{0.5}$
  Where W = weight in kg and H= height in cm

- Weight will be displayed in kilograms (kg), height will be displayed in centimeters (cm), and temperature will be displayed in Celsius (C).

- Weights, heights, or temperatures recorded in alternate units will be converted to the units being displayed using standard conversion formulas.

- Length of Hospital Stay (Days) = Date of discharge – date of hospitalization + 1

- For days on or after the device is implanted:
  Relative Study Day (Rel Day) = Date of Assessment – Date of implant + 1.

  For days before the device is implanted:
  Relative Study Day (Rel Day) = Date of Assessment – Date of implant.

- Days survived = Date of death/date of event for censoring – Date of implant + 1

- Days to explant = Date of explant – Date of initial implant + 1

- One (1) month is defined as 365.24/12

Calculation of adverse event rate per patient-year

1. Calculate the patient-years contributed by each patient. The time in the study starts at enrollment. The end date would be the last follow up date (end of study), unless the patient 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 patients in the study. Round to 2 decimal places. This is the denominator.
3. Sum the total number of events for a particular adverse event (prior to exchange). If a patient has patient-years that is missing, the AEs will not be counted for these patients (e.g., patients 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 patients in the study).

11.2 APPENDIX 2: KCCQ Determination[1]

There are 10 summary scores within the KCCQ, which are calculated as follows:

Physical Limitation

The Physical Limitation score corresponds to questions 1a through 1f. Responses to questions 1a through 1f should be coded numerically as follows:

1 = Extremely Limited
2 = Quite a bit Limited
3 = Moderately Limited
4 = Slightly Limited
5 = Not at all Limited
6 = Limited for other reasons or did not do the activity

If the responses to questions 1a through 1f are not values 1, 2, 3, 4 or 5 then the response is set to missing. Note that a response of 6 (Limited for other reasons or did not do the activity) is treated as a missing value. If at least three responses to questions 1a-1f are not missing, then the physical limitation score is computed by calculating the mean response and standardizing the result as follows:

Physical Limitation = 100*(Mean Response – 1)/4

Symptom Stability

The Symptom Stability score corresponds to question 2. Responses to question 2 should be coded numerically as follows:

1 = Much Worse
2 = Slightly Worse
3 = Not Changed
4 = Slightly Better
5 = Much Better
6 = I've had no symptoms over the last 2 weeks

If the response is 6 (no symptoms over last 2 weeks) then set the response to 3 (not changed). If question 2 is not missing then the symptom stability score is computed by standardizing the result as follows:

Symptom Stability = 100*(Response – 1)/4

Symptom Frequency

The Symptom Frequency score corresponds to questions 3, 5, 7 and 9. The responses should be coded sequentially (1, 2, 3…) in order of increasing health status as follows:

Question 3
1 = Every Morning
2 = 3 or more times per week, but not every day
3 = 1-2 times a week
4 = Less than once a week
5 = Never over the past 2 weeks

Questions 5 and 7
1 = All of the time
2 = Several times per day
3 = At least once a day
4 = 3 or more times per week, but not every day
5 = 1-2 times per week
6 = Less than once a week
7 = Never over the past 2 weeks

Question 9
1 = Every night
2 = 3 or more times a week, but not every day
3 = 1-2 times a week
4 = Less than once a week
5 = Never over the past 2 weeks

If three or more responses are missing then symptom frequency cannot be computed and will be missing. Otherwise, the symptom frequency is computed by calculating the mean of the standardized responses and multiplying by 100 as follows:

Symptom Frequency = 100*Mean((Q3 – 1)/4, (Q5 – 1)/6, (Q7 – 1)/6, (Q9 – 1)/4)

Symptom Burden

The Symptom Burden score corresponds to questions 4, 6 and 8. The responses should be coded numerically as follows:

1 = Extremely Bothersome
2 = Quite a bit Bothersome
3 = Moderately Bothersome
4 = Slightly Bothersome
5 = Not at all Bothersome
6 = I've had no swelling (fatigue, shortness of breath)

If a response is 6 (none) then set the response to 5 (not at all). If at least one response is present then symptom burden score is computed by calculating the mean response and standardizing the result as follows:

Symptom Burden = 100*(Mean Response – 1)/4

Total Symptom

The Total Symptom score is calculated as the mean of the symptom frequency score and symptom burden score.

Self-Efficacy

The Self-Efficacy score corresponds to questions 10 and 11. Responses to questions 10 and 11 should be coded sequentially (1, 2, 3, 4, 5) in order of increasing health status, with 1 denoting the

response associated with the lowest health status. If at least one question response is present then the self-efficacy score may be computed by standardizing the mean response as follows:

Self-Efficacy = 100*(Mean Response – 1)/4

Quality of Life

The Quality of Life score corresponds to questions 12, 13 and 14. Responses to questions 12, 13 and 14 should be coded sequentially (1, 2, 3, 4, 5) in order of increasing health status, with 1 denoting the response associated with the lowest health status. If at least one question response is present then the quality of life score may be computed by standardizing the mean response as follows:

Quality of Life = 100*(Mean Response – 1)/4

Social Limitation

The Social Limitation score corresponds to questions 15a through 15d. These responses should be coded numerically as follows:

1 = Severely Limited
2 = Limited Quite a bit
3 = Moderately Limited
4 = Slightly Limited
5 = Did Not Limit at All
6 = Does not apply or did not do for other reasons

If the responses to questions 15a through 15d are not values 1, 2, 3, 4 or 5 then the response is set to missing. Note that a response of 6 is treated as a missing value. If at least two question responses are present then the social limitation score may be computed by standardizing the mean response as follows:

Social Limitation = 100*(Mean Response – 1)/4

Clinical Summary

The Clinical Summary score is calculated as the mean of the physical limitation score and total symptom score.

Overall Summary

The Overall Summary score is calculated as the mean of the physical limitation score, total symptom score, quality of life score and social limitation score.

11.3 APPENDIX 3: EuroQol 5D-5L Determination

The EQ-5D™ has two parts. The first part is a descriptive system that classifies respondents into one of 243 distinct health states. The descriptive system consists of the following five dimensions:

1. Mobility (MO).
2. Self-care (SC).
3. Usual activities (UA).
4. Pain/discomfort (PD).
5. Anxiety/depression (AD).

Each dimension has five possible levels (i.e., 1 to 5), representing "no problems," "slight problems", "moderate problems", "severe problems", and "unable to/extreme problems" respectively. Respondents are asked to choose one level that reflects their "own health state today" for each of the five dimensions. This health state classifier can describe 3125 unique health states that are often reported as vectors ranging from 11111 (full health) to 55555 (worst health).

The second part is a 20-cm visual analog scale (EQ-VAS) that has endpoints labeled "best imaginable health state" and "worst imaginable health state" anchored at 100 and 0, respectively. Respondents are asked to indicate how they rate their own health by drawing a line from an anchor box to that point on the EQ-VAS which best represents their own health on that day. Hence, the EQ-5D™ produces three types of data for each respondent:

1. A profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor (e.g., 11121, 33211)
2. A population preference-health index value based on the descriptive system.
3. A self-reported assessment of health status based on the EQ-VAS.

Missing values should be left blank. The index value will not be calculated when responses are missing for one or more of the dimensions.

EQ-5D-5L health states, defined by the EQ-5D-5L descriptive system, may be converted into a single index value. The index values, presented in country specific value sets, are a major feature of the EQ-5D instrument, facilitating the calculation of quality-adjusted life years (QALYs) that are used to inform economic evaluations of health care interventions.
By using the crosswalk link function and the individual responses to the EQ-5D-5L descriptive system, index values for the EQ-5D-5L can be calculated.

[redacted]

[redacted]

12 REFERENCES

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