STATISTICAL ANALYSIS PLAN

Protocol OCS-CAR-012014

International Trial to Evaluate the Safety and Effectiveness of the Portable Organ Care System (OCS™) Heart for Preserving and Assessing Expanded Criteria Donor Hearts for Transplantation (EXPAND Heart Trial)

September 21, 2018

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Study Number: OCS-CAR-012014

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Table of Contents

List of Tables

List of Tables (continued)

List of Supplemental Tables

List of Listings

List of Abbreviations

Term	Definition
AE	Adverse Event
AOF	Aortic Flow
AOP	Aortic Pressure
BiVAD	Bilateral Ventricular Assist Device
BMI	Body Mass Index
CAD	Coronary Artery Disease
CEC	Clinical Events Committee
CF	Cardiac Flow
CI	Cardiac Index
CI	Confidence Interval
CO	Cardiac Output
CPR	Cardiopulmonary Resuscitation
ECG	Electrocardiogram
ECHO	Echocardiogram
ECMO	Extracorporeal Membrane Oxygenation
EF	Ejection Fraction
EPROM	Erasable Programmable Read Only Memory
HCO_3	Bicarbonate
HR	Heart Rate
IABP	Intra-aortic Balloon Pump
ICU	Intensive Care Unit
IL2	Interleukin 2
ISHLT	International Society for Heart and Lung Transplantation
IVSd	Intraventricular Septum thickness at end-diastole
LAP	Left Atrial Pressure
LV	Left Ventricular
LVAD	Left Ventricular Assist Device
LVED	Left Ventricular End Diastolic
LVEF	Left Ventricular Ejection Fraction
LVES	Left Ventricular End Systolic
MAP	Mean Arterial Pressure
MedDRA	Medical Dictionary for Regulatory Activities
OCS™	Organ Care System
OPTN	Organ Procurement and Transplantation Network
OR	Operating Room
PAP	Pulmonary Artery Pressure
PCO_2	Pulmonary Carbon Dioxide Pressure
PF	Peak Flow
PGD	Primary Graft Dysfunction
pH	Hydrogen Ion Concentration
PO_2	Partial Pressure of Oxygen
PT	Preferred Term
PCWP	Pulmonary Capillary Wedge Pressure
PWTd	Posterior Wall Thickness at end-diastole
RAP	Right Atrial Pressure
RBC	Red Blood Cell

List of Abbreviations (continued)

RV	Right Ventricular
RVAD	Right Ventricular Assist Device
RVSP	Right Ventricular Systolic Pressure
SAE	Serious Adverse Event
SDS	Same Day Surgery
SOC	System Organ Class
SvO_2	Venous Oxygen Saturation
T0, T24, T48, T72	Time after transplant (0, 24, 48 and 72 hours)
TPG	Transpulmonary Gradient
US	United States
VAD	Ventricular Assist Device

1.0 INTRODUCTION

This analysis plan gives a detailed description of the safety and effectiveness analyses, summary tables, and by-patient data listings planned in the analysis of the data in the OCS-CAR-012014 study ["International Trial to Evaluate the Safety and Effectiveness of the Portable Organ Care System (OCS™) Heart for Preserving and Assessing Expanded Criteria Donor Hearts for Transplantation (EXPAND Heart Trial)"].

Over the last two decades heart transplantation has evolved as the gold standard for treating end-stage heart failure[1-3]. While the demand for heart transplantation globally has increased significantly each year, the utilization or recovery of available donor hearts for transplantation has been limited to approximately 30% of the annual available pool of donor hearts in the US[4]. Based on the Organ Procurement and Transplantation Network (OPTN) 2011 report, approximately 4,600 consented, donor hearts in the US are not transplanted annually, depriving thousands of patients the gift of new hearts to treat their end-stage heart disease. The main cause for these unfortunate circumstances is that the current technique for heart preservation using cold flush and storage has the following severe limitations:

- It subjects the donor hearts to significant time-dependent ischemic injury[5] and subsequent reperfusion injury that impair heart function post-transplant. This causes transplanting physicians to only select for procurement those hearts most likely to withstand the potential damage associated with cold storage preservation. It also imposes significant time and geographical limitations on the heart retrieval process, adversely impacting the utilization of available donor hearts. In addition, this time-dependent ischemic injury has been directly correlated to post-transplant complications.

- It lacks any perfusion capabilities to maintain the heart in a near-physiologic[6] *(in-vivo-like)* environment after the donor heart is retrieved from the body of the donor. This limitation results in significant underutilization of the donor heart pool given that many donor hearts are subject to the negative impact of brain death and other untoward physiological conditions in the body of the donor, prior to their procurement.

- It lacks any ability to evaluate organ metabolic state and function after procurement and preservation to determine the suitability of the donor hearts for transplantation. This significantly limits the utilization of donor hearts that are subjected to negative, non-physiologic conditions of brain death in the donor.

This severe imbalance between supply and demand for donor hearts has resulted in the significant rise of the use of Left Ventricular Assist Devices (LVADs) over the past few years. This rise in VAD use is associated with significant economic burden to the healthcare system driven by the rate of clinical complications and the potential need for more than one VAD implant due to pump thrombosis or malfunction, while survival benefits are still well below the ones achieved by a heart transplantation procedure.

More importantly, annually this severe underutilization results in >25% of the patients listed on the national waiting list for heart transplantation dying or deteriorating in health condition while awaiting to receive a heart transplantation.

Poor organ function is the primary reason why consented donor hearts are not utilized. Poor organ function is often a result of the non-physiologic conditions that occur in the body of the donor following brain death and subsequent mechanical ventilation dependency, rather than a physiological impairment of the organ. The ability to remove these donor organs from these harsh conditions in the donor and to preserve them in a healthy *in-vivo-like* environment has been shown to improve donor heart function ex-vivo. Such preservation is not possible with cold, ischemic storage.

Another common reason for not utilizing donor organs is that no recipient was found. This is often a result of (1) the limited time allowed for transportation of the donor organ to the recipient, which is limited by the ischemic and reperfusion injuries known to occur with cold, ischemic storage conditions and/or (2) the inability to measure organ function ex vivo to evaluate the organ's function.

Over the past 8+ years, there has been a global focus on *ex-vivo* organ perfusion in a near physiologic condition as a promising technique to overcome the current challenges in organ preservation and to potentially increase utilization of donor organs (heart, lung, liver and kidney) that are currently not used due to shortcomings of cold storage[7].

Currently, the TransMedics Organ Care System (OCS™) Heart technology is the only portable system available for ex-vivo maintenance of the donor heart in a metabolically active and beating state. The portable Organ Care System (OCS™) Heart is intended to significantly reduce ischemia and reperfusion injuries to the donor heart and enable immediate physiologic preservation, optimization of donor heart environment, and metabolic assessment of donor heart perfusion to assess its suitability for transplantation.

The OCS™ Heart enables the donor heart to be maintained in a near physiologic functioning state ex-vivo, continuously perfused with a warm, oxygenated and nutrient-enriched blood (cellular)-based perfusate. The OCS™ Heart may enable the following clinical advantages:

- Reduction of the time-dependent ischemic injury[8] to the donor hearts during preservation, thus eliminating significant logistical and geographical barriers to heart transplantation that currently exist with cold storage preservation.
- Optimization of the donor heart ex-vivo environment by optimizing oxygen and substrate delivery, while also replenishing key hormones and nutrients that are depleted due to the brain death condition in the body of the donor and would negatively impact cardiac function if not replenished.
- Assessing the adequacy of the perfusion on donor heart utilizing standard lactate levels to allow physicians to judge the suitability of the organ for transplantation using the standard criteria that physicians currently use when harvesting the organ from the donor, thus substantially minimizing the risk of transplanting poor hearts into recipients.

2.0 STUDY OBJECTIVE

The objective of this study is to evaluate the safety and effectiveness of the OCS™ Heart to recruit, preserve and assess donor hearts that may not meet current standard donor heart acceptance criteria based on one or more of the following criteria:

- Expected total cross-clamp time of ≥ 4 hours
- Expected total cross-clamp time of ≥ 2 hours PLUS one or more of the following risk factors:
    - Donor is between 45-55 years old with no coronary catheterization data, or
    - Donor age is ≥ 55 years, or
    - Left ventricular septal or posterior wall thickness of > 12 mm and ≤ 16 mm, or
    - Reported down time of ≥ 20 minutes, with stable hemodynamics at the time of final assessment, or
    - Left heart ejection fraction (EF) ≥ 40% and ≤ 50%, or
    - Donor angiogram with luminal irregularities with no significant coronary artery disease (CAD), or
    - History of carbon monoxide poisoning with good cardiac function at time of donor assessment, or
    - Social history of alcoholism with good cardiac function at time of donor assessment, or
    - History of diabetes combined with negative coronary angiogram for CAD

3.0 STUDY DESIGN

3.1 Overview

This is a prospective, pivotal, international, single-arm trial of donor hearts and donor heart transplant recipients. This trial will be conducted at no more than 20 institutions in the United States and world-wide (Europe, Australia, and Canada) and will include up to 75 transplanted heart recipients.

The Schedule of Clinical Assessments for the donor and recipient is provided in Table 1.

Table 1: Schedule of Clinical Assessments

Evaluations	Donor & Heart Assessments	
	Acceptance	OCS Preservation
Eligibility & ID	X	
Demographics/Characteristics	X	
Donor Cause of Death	X	
Donor Medical & Social History	X	
Donor Heart Assessment	X	
Donor Cross Clamp Time and Flush Detail	X	
OCS Preservation Parameters		X
OCS Lactate Levels		X
Device Malfunction (if applicable)		X
Non-transplant Reasons (if applicable)		X

Evaluations	Recipient Schedule of Assessments									
	Day of Tx	T 0^	T 24	T 48	T 72	Day 7	Discharge	Day 30	Month 6	Month 12
Eligibility & Informed Consent	X									
Demographic/Characteristics	X									
Medical & Cardiac History	X									
Transplant Details	X									
PGD Scores			X							
Inotropes Support Dose		X	X	X	X					
Right heart Catheter Data*		X	X	X	X					
Mechanical Circulatory Support		X	X	X	X	X				
Invasive Ventilator Support		X	X	X	X	X				
Patient Survival								X	X	X
Graft Survival								X	X	X
Post-Transplant ECHO*							X			
Immunosuppressive Meds & Induction (if applicable)	X					X	X			
ICU & Hospital Stay		X	X	X	X	X	X			
Heart Graft-Related AEs & SAEs	X	X	X	X	X	X	X	X		
Coronary Angiogram Results*										X

^ T0 is defined as the time of initial admission to ICU immediately post-heart transplant procedure
* ONLY tests regularly scheduled per center standard of care or performed due to a clinical cause at these time-points will be collected.

3.2 Method of Assigning Subjects to Treatment

Not applicable.

3.3 Blinding

Not applicable.

3.4 Determination of Sample Size

The sample size for this trial was determined based on the primary effectiveness composite endpoint of patient survival at Day 30 post-transplantation and absence of severe primary graft dysfunction (PGD) (left or right ventricle) in the first 24 hours post-transplantation. The primary statistical hypotheses to be tested are as follows:

$$H_0: \pi \leq 0.65 \quad \text{and}$$

$$H_1: \pi > 0.65,$$

where π is the true proportion of transplanted recipients with patient survival at day 30 post-transplantation and absence of severe PGD (left or right ventricle) in the first 24 hours post-transplantation. A one-sided exact binomial test will be performed to test the null hypothesis. The sample size calculations assumed an alpha level of 0.05, a Performance Goal of 0.65, a true primary endpoint proportion for OCS™ of 0.80, and power of 80%. Based on these specifications, the required sample size was determined to be 55 transplanted recipients. Assuming that there are exactly 55 transplanted recipients in the study, the null hypothesis will be rejected only if at least 76.4% (i.e., 42 of the 55 recipients) meet the primary endpoint. In order to increase the statistical power, the sample size was increased to 75 transplanted recipients.

3.5 Changes to the Protocol-Specified Analyses

No changes were made to the protocol-specified analyses.

4.0 EFFECTIVENESS AND SAFETY ENDPOINTS

All effectiveness and safety endpoints based on PGD results will use the adjudicated results.

4.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is a composite endpoint of patient survival at Day 30 post-transplantation and absence of severe PGD (left or right ventricle) in the first 24 hours post-transplantation.

4.2 Secondary Effectiveness Endpoints

The secondary effectiveness endpoints are as follows:

- Patient survival at Day 30 post-transplantation
- Incidence of severe primary graft dysfunction (PGD) (left or right ventricle) in the first 24 hours post-transplantation
- Rate of donor hearts utilization that were successfully transplanted after preservation and assessment on the OCS^{TM} heart device

4.3 Other Effectiveness Endpoints

Another effectiveness endpoint is a composite of patient survival at Day 30 post-transplantation and within initial hospital discharge and absence of severe PGD (left or right ventricle) in the first 24 hours post-transplantation.

4.4 Safety Endpoint

The safety endpoint is the number of heart graft-related serious adverse events in the first 30 days post-transplantation per subject. This endpoint is defined to consist of the following adverse events (at most one per type), if they are serious adverse events:

- Moderate or severe Primary Graft Dysfunction (PGD) (left or right ventricle) (not including rejection or cardiac tamponade). Please see Appendix 2 of the protocol for detailed definitions of LV and RV PGD according to ISHLT consensus manuscript.
- Primary graft failure requiring re-transplantation.

5.0 STATISTICAL CONSIDERATIONS

5.1 General Methodology

All statistical analyses will be performed and all tables and listings will be produced using SAS® Version 9.4 or higher.

Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized using frequencies and percentages. All statistical tests will be performed at the 0.05 significance level.

All data collected will be included in the data listings. Data listings will be sorted either by recipient ID or by donor organ ID, as appropriate. All date fields will be presented in a format of ddmmmyyyy (e.g., 01Jan2017) in the listings.

5.2 Adjustments for Covariates

If there are any missing data for the primary effectiveness endpoint, multiple imputation methods will be used to impute missing data. The logistic regression method of imputation will be used with covariates for various baseline characteristics (to be specified). No other adjustments for covariates will be made in the statistical analyses.

5.3 Handling of Dropouts and Missing Data

If there are any missing data for the primary efficacy endpoint, multiple imputation methods will be used to impute missing data for this endpoint. No imputation will be performed for any other effectiveness or safety outcome.

5.4 Interim Analyses and Data Monitoring

No interim analyses will be performed.

5.5 Multicenter Studies

Subjects will be recruited from up to twenty investigative sites in the US and worldwide (Europe, Australia, and Canada).

5.6 Multiple Comparisons / Multiplicity

No adjustments for multiple comparisons/multiplicity will be made.

5.7 Examination of Subgroups

Recipient height and weight will be summarized, stratified by gender, for the Transplanted Recipient Population in Supplemental Table 2.1. Subgroup analyses of the primary effectiveness endpoint will be analyzed for the following subgroups:

- Donor inclusion criteria:
    - Donor Expected Total Cross-Clamp Time ≥ 4 Hours
    - Donor Expected Total Cross-Clamp Time ≥ 2 Hours AND each of the following (9 subgroups, which may overlap):

1) Donor between 45-55 Years Old with No Coronary Catheterization Data;
2) Donor Age is ≥ 55 Years;
3) Donor Left Ventricular Septal or Posterior Wall Thickness > 12 mm and ≤ 16 mm;
4) Donor Reported Down Time ≥ 20 Minutes with Stable Hemodynamics at Time of Final Assessment;
5) Donor Left Heart Ejection Fraction ≥ 40% and ≤ 50%;
6) Donor Angiogram with Luminal Irregularities with No Significant CAD;
7) Donor Cause of Death by Carbon Monoxide Poisoning with Good Cardiac Function at Time of Donor Assessment;
8) Donor Social History of Alcoholism with Good Cardiac Function at Time of Donor Assessment; and
9) Donor History of Diabetes Combined with Negative Coronary Angiogram for CAD

- Primary etiology of recipient heart failure diagnosis (ischemic cardiomyopathy, congenital heart disease, restrictive cardiomyopathy, and other)

6.0 ANALYSIS POPULATIONS

The Transplanted Recipient Population will consist of all recipients who are transplanted according to the OCS™ Heart protocol and who have no major protocol violations. The analyses of all effectiveness and safety endpoints, except the rate of donor hearts utilization that were successfully transplanted after preservation and assessment on the OCS™ heart device, will be based on the Transplanted Recipient Population.

For this study, major protocol violations include:
- Donor and recipient's Inclusion/Exclusion Criteria Violation
- Failure to follow IFU
- Failure to follow protocol

The OCS™ Heart Population will consist of all donor hearts that are transported by the OCS™. The analysis of the rate of donor hearts utilization that were successfully transplanted after preservation and assessment on the OCS™ heart device will be based on the OCS™ Heart Population.

7.0 SUBJECT AND DONOR HEART DISPOSITION

The numbers of subjects in the following categories will be presented in Table 1.1:

- Signing the informed consent
- Not matched with an EXPAND heart
- Matched with an EXPAND heart
- Matched with an EXPAND heart turned down after OCS™
- Matched with an EXPAND heart accepted for transplant after OCS™ but not transplanted
- In the Transplanted Recipient Population

The table will also present the number and percentage of Transplanted Recipient Population patients who completed the study, who died on study, who withdrew from the study early, both overall and by time period (before day 30, between day 30 and 6 months, and between 6 months and 12 months), and the reason for withdrawal.

Donor heart disposition and acceptance details will be summarized in Table 1.2 for the OCS™ Heart Population using frequencies and percentages.

8.0 PROTOCOL DEVIATIONS

Protocol deviations will be summarized for the Transplanted Recipient Population by type of deviation and overall in Table 1.3 using counts and percentages.

9.0 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Recipient demographic and baseline characteristics will be summarized for the Transplanted Recipient Population in Table 2.1. Frequencies and percentages will be presented for gender, ethnicity, race, and blood type. Descriptive statistics will be presented for age, height, weight, body mass index, and panel reactive antibody. Recipient height and weight will also be summarized, stratified by gender, for the Transplanted Recipient Population in Supplemental Table 2.1.

Cardiac medical history (Table 2.2) and non-cardiac medical history (Table 2.3) at screening will be summarized for the Transplanted Recipient Population using descriptive statistics for continuous variables and frequencies and percentages for categorical variables.

Donor demographics, baseline characteristics, and inclusion criteria will be summarized in Table 2.4.1 for the Transplanted Recipient Population and in Supplemental Table 2.4.1 for the OCS™ Heart Population. Frequencies and percentages will be presented for gender, ethnicity, race, blood type, and donor inclusion criteria. Descriptive statistics will be presented for age, height, weight, and body mass index.

Inclusion-related donor demographic and baseline characteristics (Table 2.4.2) will be summarized by donor inclusion criteria for the Transplanted Recipient Population using descriptive statistics.

The number and percentage of subjects in each donor inclusion criterion group will be presented in Table 2.4.3 for the Transplanted Recipient Population.

Donor medical history will be summarized for the Transplanted Recipient Population in Table 2.5 and for the OCS™ Heart Population in Supplemental Table 2.5 using frequencies and percentages.

Donor cause of death (cerebrovascular hemorrhage, head trauma, or other), whether there was chest trauma, whether there was any evidence of sternum fractures, whether there was any evidence of rib fractures, whether there was any evidence of RV contusions, whether there was any evidence of LV contusions, whether the donor experienced cardiac arrest, and whether the cardiac arrest was witnessed will be summarized in Table 2.6 for the Transplanted Recipient Population and in Supplemental Table 2.6 for the OCS™ Heart Population using frequencies and percentages. The duration of cardiac arrest will be summarized using descriptive statistics.

Angiogram and donor management data at the final donor acceptance assessment will be summarized for the Transplanted Recipient Population in Table 2.7 and for the OCS™ Heart Population in Supplemental Table 2.7 using descriptive statistics for continuous variables and frequencies and percentages for categorical variables.

Final donor offer echocardiogram test results will be summarized for the Transplanted Recipient Population in Table 2.8 and for the OCS™ Heart Population in Supplemental Table 2.8 using descriptive statistics for continuous variables and frequencies and percentages for categorical variables.

Donor heart baseline chemistry test results will be summarized for the Transplanted Recipient Population in Table 2.9 and for the OCS™ Heart Population in Supplemental Table 2.9 using descriptive statistics.

10.0 OCS™ PRESERVATION CHARACTERISTICS

OCS™ perfusion time and ischemia time will be summarized using descriptive statistics in Table 3.1 for the Transplanted Recipient Population and in Supplemental Table 3.1 for the OCS™ Heart Population. Donor heart chemistry data on OCS™ instrumentation will be summarized by time point (pre-instrumentation, initial OCS™ instrumentation, and final OCS™ instrumentation) using descriptive statistics in Table 3.2 for the Transplanted Recipient Population and in Supplemental Table 3.2 for the OCS™ Heart Population. Donor heart assessment post OCS™ preservation will be summarized using frequencies and percentages in Table 3.3 for the Transplanted Recipient Population and in Supplemental Table 3.3 for the OCS™ Heart Population.

Device malfunction data will be summarized for the OCS™ Heart Population using frequencies and percentages in Table 3.4.

11.0 TRANSPLANT CHARACTERISTICS AND ICU AND HOSPITAL STAYS

Table 3.5 will summarize transplant characteristics for the Transplanted Recipient Population using descriptive statistics for continuous variables and frequencies and percentages for categorical variables.

Table 5.5 will summarize the post-transplant ICU stay for the Transplanted Recipient Population using descriptive statistics for the initial ICU stay and the re-admission ICU stay duration, and using the frequency and percentage for whether the recipient was readmitted to the ICU.

Table 5.6 will summarize the post-transplant hospitalization for the Transplanted Recipient Population using descriptive statistics for the initial hospital stay duration and the frequency and percentage for whether the recipient was re-hospitalized within the first 30 days post-transplant.

12.0 EFFECTIVENESS ANALYSES

All PGD based effectiveness endpoints will be based on the recipient adjudicated primary graft surveillance data.

12.1 Primary Effectiveness Analyses

The primary hypothesis for this study is that the true (success) proportion of transplanted patients meeting the primary effectiveness endpoint, patient survival at day 30 post-transplantation and absence of severe PGD (left or right ventricle) in the first 24 hours post-transplantation, is greater than the Performance Goal value of 0.65. The primary statistical hypotheses are as follows:

$$H_0: \pi \leq 0.65 \text{ and}$$

$$H_1: \pi > 0.65,$$

where π is the true proportion of transplanted recipients with patient survival at day 30 post-transplantation and absence of severe heart PGD (left or right ventricle) in the first 24 hours post-transplantation.

It is unlikely that there will be any missing data for the primary effectiveness endpoint. If there are no missing data, this endpoint will be summarized using counts and percentages and an exact 95% confidence interval for the true percentage based on the binomial distribution. A one-sided exact binomial test will be performed to test the null hypothesis H_0.

If there are any missing data for this endpoint, it will be analyzed using multiple imputation methods to impute any missing data. Using SAS® PROC MI, the logistic regression method of imputation will be used with terms for various baseline characteristics (to be specified) and the primary endpoint. This method of multiple imputation is appropriate for a binary dependent variable with explanatory variables following a monotone missing pattern and assumes that the data for the dependent variable are missing at random (MAR). If the variables do not exhibit a monotone missing pattern, missing data will instead be imputed using the fully conditional specification (FCS) approach of SAS® PROC MI. Twenty imputation data sets will be generated. For each imputed dataset, PROC FREQ of SAS® will be used to obtain the success proportion and the corresponding standard error. PROC MIANALYZE of SAS® will be used to combine the results from the imputed datasets to produce an overall estimate of the true success proportion and the corresponding 95% confidence interval. The p-value for the test of the null hypothesis from a normal approximation test will also be presented. The results will be summarized in Table 4.1.1.

A site effect analysis based on the non-imputed data will be conducted to assess the poolability of data for the primary effectiveness endpoint. For this analysis, sites with fewer than five subjects will be grouped into a single, larger Analysis Site. A chi-square test will be performed to test the null hypothesis that the true proportion of transplanted patients meeting the primary effectiveness endpoint does not vary by site. A 0.15 significance level will be used for this test. If the p-value < 0.15, then an analysis adjusting for site will be considered. Table 4.1.2 will present the observed success proportion and corresponding exact 95% confidence interval for the true success proportion for each site.

12.2 Secondary Effectiveness Analyses

The secondary effectiveness endpoints are as follows:

1. Patient survival at Day 30 post-transplantation
2. Incidence of severe primary graft dysfunction (PGD) (left or right ventricle) in the first 24 hours post-transplantation
3. Rate of donor hearts utilization that were successfully transplanted after preservation and assessment on the OCS™ heart device

These endpoints will be summarized using frequencies and percentages and exact (Clopper-Pearson) 95% confidence intervals for the true population percentages. The first two secondary effectiveness endpoints will be analyzed based on the Transplanted Recipient Population (Table 4.1). The third endpoint, which is the ratio of the number of successfully transplanted donor hearts divided by the number of donor hearts in the OCS™ Heart Population, will be analyzed based on the OCS™ Heart Population (Table 4.1).

12.3 Other Effectiveness Analyses

The composite endpoint, patient survival at day 30 post-transplantation and within initial hospital discharge and absence of severe PGD (left or right ventricle) in the first 24 hours post-transplantation, will be summarized (Table 4.2) overall and by individual component using counts and percentages and an exact (Clopper-Pearson) 95% confidence interval for the true population percentage.

Table 4.3 will present Kaplan-Meier estimated survival time probabilities for the following nominal time points: Day 30, Month 6, and Month 12.

13.0 SAFETY ANALYSES

13.1 Adverse Events

Only serious adverse events and heart graft-related adverse events will be reported.

Safety will be analyzed principally by examination of the frequency of adverse events. In particular, the number of heart graft-related serious adverse events (SAEs) in the first 30 days post-transplantation per subject will be analyzed. This endpoint is defined to consist of the following adverse events (at most one per type), if they are serious adverse events:

- Moderate or severe Primary Graft Dysfunction (PGD) (left or right ventricle) (not including rejection or cardiac tamponade):. Please see Appendix 2 of the protocol for detailed definitions of LV and RV PGD according to ISHLT consensus manuscript.
- Primary graft failure requiring re-transplantation

This endpoint will be summarized using descriptive statistics and a 95% confidence interval for the mean based on the t-distribution (Tables 6.1).

In addition, the numbers and percentages of subjects experiencing at least one serious adverse event (AE), at least one heart graft-related AE, at least one severe heart graft-related AE, at least one device-related heart graft-related AE (AEs that are probably or definitely related to the investigational device or for which the relationship is missing), at least one unanticipated heart graft-related AE, and at least one heart graft-related serious AE, and the number and percentage of deaths will be tabulated (Table 6.2). Also, the number of heart graft-related AEs and the number and percentage of subjects experiencing heart graft-related AEs will be tabulated by system organ class (SOC) and preferred term (PT) using MedDRA (Table 6.3). Similarly, the number of SAEs and the number and percentage of subjects experiencing SAEs will be tabulated by system organ class (SOC) and preferred term (PT) using MedDRA (Table 6.4), and the number of heart graft-related serious AEs and the number and percentage of subjects experiencing heart graft-related serious AEs will be tabulated by SOC and PT using MedDRA (Table 6.5). The number and percentage of heart graft-related AEs will be tabulated by SOC and PT and the relationship of the adverse event to the device (related versus not related, where AEs with a probable or definite relationship to the investigational device are classified as related, and AEs with a possible, unlikely, or unrelated relationship are classified as not related) (Table 6.6) and by SOC and PT and severity (Table 6.8). The number and percentage of subjects experiencing heart graft-related AEs will be tabulated by SOC and PT and the relationship of the adverse event to the device (related versus not related) (Table 6.7) and by SOC and PT and severity (Table 6.9).

13.2 Medications (medications related to Serious Adverse Events only)

Table 7.1 will present the number and percentage of subjects in the Transplanted Recipient Population using each type of immunosuppressive induction, and Table 7.2 will present the number and percentage of subjects in the Transplanted Recipient Population using each type of immunosuppressive medication.

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14.0 OTHER ANALYSES

Post-transplant invasive hemodynamics data will be summarized using descriptive statistics by time point (T0, T24, T48, and T72) (Table 5.1). Post-transplant inotopic support at the time of invasive hemodynamics will be summarized by time point (T0, T24, T48, and T72) and type of support using counts and percentages (Table 5.2).

Echocardiogram data at hospital discharge will be summarized (Table 5.3) using descriptive statistics for continuous variables and frequencies and percentages for categorical variables. Post-transplant echocardiogram data at transplant and post-transplant time points will be summarized (Table 5.4) using descriptive statistics for continuous variables and frequencies and percentages for categorical variables.

Primary graft dysfunction surveillance data at 24 hours post-transplant will be summarized (Table 5.7) using frequencies and percentages.

Recipient data at the 30 day follow-up visit will be summarized using counts and percentages in Table 5.8. Recipient data at the 6 month (Table 5.9) and 12 month (Table 5.10) follow-up visits [was the patient withdrawn from the study since the last visit and, if so, the reason for withdrawal; did the recipient survive; did the heart graft survive, and, if not, the action taken with respect to the recipient; was there a diagnosis of cardiac dysfunction since the last visit; was recipient re-hospitalized; was a standard of care coronary angiogram performed (12 months only); and was a standard of care right heart catheterization performed (12 months only)] will be summarized using frequencies and percentages.

Table 5.11 will summarize initial invasive post-transplant ventilator support data using descriptive statistics for the duration of support and the frequency and percentage for where the patient's final extubation occurred. Table 5.12 will summarize post-transplant mechanical circulatory support data using descriptive statistics for continuous variables (duration of support) and frequencies and percentages for categorical variables.

These analyses will be performed for the Transplanted Recipient Population.

Analyses associated with the OCS™ trend files will consider start time according to the following:

- Cardiac Flow (CF): After perfusion start time (perfusion time = 0:02) when the measure first equals or exceeds a value of 0.10
- For all other parameters: After perfusion start time (perfusion time = 0:02)

Finish time will be at the end of perfusion incorporating the cooling process.

15.0 REFERENCES

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APPENDIX A: TABLE SHELLS

APPENDIX B: LISTING SHELLS