INVESTIGATIONAL PLAN/PROTOCOL

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)

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CONFIDENTIAL – PROPRIETARY INFORMATION

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OCS™ HEART EXPAND TRIAL SYNOPSIS

Protocol Title	International Trial to Evaluate the Safety and Effectiveness of The Portable Organ Care System (OCS™) Heart for Recruiting, Preserving and Assessing Expanded Criteria Donor Hearts for Transplantation (EXPAND Heart Trial)
Intended Use	The OCS™ Heart is to be used to recruit, preserve and assess donor hearts that may not meet current standard donor heart acceptance criteria for transplantation from one or more of the following characteristics: • 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 age 45-55 years old with no coronary catheterization data, or – Donor age ≥ 55 years old; or – Left ventricular septal or posterior wall thickness of >12 ≤ 16 mm; or – Reported down time of ≥20 min, with stable hemodynamics at time of final assessment; or – Left heart ejection fraction (EF) ≥ 40 ≤ 50%; or – Donor angiogram with luminal irregularities with no significant CAD – History of Carbon monoxide poisoning with good cardiac function at time of donor assessment – Social history of alcoholism with good cardiac function at time of donor assessment; or – History of diabetes combined with negative coronary angiogram for coronary artery disease (CAD).
Objectives	To evaluate the effectiveness of the OCS™ Heart to recruit, preserve and assess donor hearts that may not meet current standard donor heart acceptance criteria (as identified above) for transplantation to potentially improve donor heart utilization for transplantation
Trial Design	A prospective, pivotal, international single-arm trial
Trial Size	A maximum of 20 participating sites worldwide with 75 transplanted heart recipients
Screening and Treatment	Donor hearts will be screened for trial eligibility. Eligible donor hearts will be recruited, preserved and assessed with the Organ Care System (OCS™). After OCS™ recruitment, preservation and assessment, trial donor hearts will be evaluated for acceptability for transplantation. Primary heart transplant candidates will be screened for trial eligibility. Every eligible candidate will be asked to participate. Eligible heart transplant candidates will receive OCS™ preserved donor hearts that have been deemed clinically acceptable for transplantation by the treating transplant clinical team.
Donor Heart Eligibility Criteria	**Inclusion** At least one of the following: • Expected total cross-clamp time of ≥ 4 hours • Expected total cross-clamp time of ≥ 2 hours **PLUS** one of the following risk factors: – Donor age 45-55 years old with no coronary catheterization data, or – Donor age ≥ 55 years old; or – Left ventricular septal or posterior wall thickness of >12 ≤16 mm; or – Reported down time of ≥ 20 min, with stable hemodynamics at time of final assessment; or – Left heart ejection fraction (EF) ≥ 40 ≤ 50%; or – Donor angiogram with luminal irregularities with no significant CAD – History of Carbon monoxide poisoning with good cardiac function at time of donor assessment – Social history of alcoholism with good cardiac function at time of donor assessment; or – History of diabetes combined with negative coronary angiogram for coronary artery disease (CAD).

	Exclusion • Angiogram proven CAD with >50% stenosis, or • Cardiogenic shock or myocardial infarction, or • Sustained terminal EF of <40%, or • Significant valve disease except for competent bicuspid aortic valve.
Recipient Eligibility Criteria	**Inclusion** • Registered male or female primary Heart transplant candidate • Age ≥ 18 years old • Signed: 1) written informed consent document and 2) authorization to use and disclose protected health information. **Exclusion** • Prior solid organ or bone marrow transplant • Chronic use of hemodialysis or diagnosis of chronic renal insufficiency • Multi-organ transplant.

Donor Heart on OCS™ Transplant Criteria	**Accept for Transplantation**
	Donor hearts preserved on the OCS™ should be maintained within the following parameters:
	• Total OCS™ arterial Lactate level < 5 mmol/L
	• Stability of OCS™ Heart Perfusion Parameters within ranges:
	  ○ CF 400-900 ml/min
	  ○ AOP 40-100 mmHg
	
	Reject for Transplantation
	• Total OCS™ arterial Lactate Level >5 mmol/L at the end of OCS™ perfusion period
	• Transplanting surgeon/heart failure cardiologist clinically unsatisfied with donor heart evaluation on OCS™ (If yes, specify reason).

Primary Endpoint	A composite endpoint of patient survival at Day-30 post-transplant and absence of severe primary heart graft dysfunction (PGD) (left or right ventricle) in the first 24 hours post-transplantation.
Secondary Endpoints	• Patient survival at day-30 post-transplantation. • Incidence of severe primary heart 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™ heart device.
Safety Endpoint	Incidence of heart graft-related Serious Adverse Events (SAEs) in the first 30 days post heart transplantation, defined as: • Moderate or Severe primary heart graft dysfunction (PGD) (left or right ventricle) (not including rejection or cardiac tamponade). Please see Appendix 2 for detailed definition of LV and RV PGD according to ISHLT consensus manuscript. Primary graft failure requiring re-transplantation.
Follow-up	All patients will be followed for up to 1 year post-transplant.
Statistical Methods	**Analysis Populations** The transplanted recipient population will consist of all recipients who are transplanted according to this 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 assessments on the OCS™ heart device, will be based on the transplanted recipient population. 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.

	Effectiveness The primary hypothesis for this trial is that the true proportion of transplanted recipients with composite patient survival at Day 30 post-transplantation and absence of severe primary heart graft dysfunction (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: $\pi \leq 0.65$ and H_1: $\pi > 0.65$, where π is the true proportion of transplanted recipients with patient survival at Day 30 and absence of severe primary heart graft dysfunction (PGD) (left or right ventricle) in the first 24 hours post-transplantation The primary effectiveness 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 at the 0.05 significance level will be performed to test the null hypothesis H_0. The secondary effectiveness endpoints for this trial are as follows: • Patient survival at day-30 post-transplantation • Incidence of severe primary heart graft dysfunction (PGD) (left or right ventricle) in the first 24 hours post-transplantation • Rate of donor hearts utilization from above characteristics that were successfully transplanted after preservation and assessment on the OCS™ heart device. Each secondary effectiveness endpoint will be summarized using counts and percentages and an exact 95% confidence interval for the true percentage based on the binomial distribution. **Safety** 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) up to the 30-day follow-up after 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 heart graft dysfunction (PGD) (left or right ventricle) (not including rejection or cardiac tamponade). Please see Appendix 2 for detailed definition of LV and RV PGD according to ISHLT consensus manuscript. • Primary graft failure requiring re-transplantation. This endpoint will be summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum, maximum, and a 95% confidence interval for the mean based on the t-distribution.
Determination of Sample Size	The sample size for this trial was determined based on the primary effectiveness endpoint, patient survival at Day 30 and absence of severe primary heart graft dysfunction (PGD) (left or right ventricle) in the first 24 hours post-transplantation. The calculation assumed a one-sided exact binomial test, an alpha level of 0.05, a Performance Goal of 0.65, a true survival rate for OCS™ of 0.8, 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 effectiveness endpoint.
Trial Sponsor	TransMedics, Inc. 200 Minuteman Road, Suite 302 Andover, MA, USA 01810

1. INTRODUCTION AND BACKGROUND INFORMATION

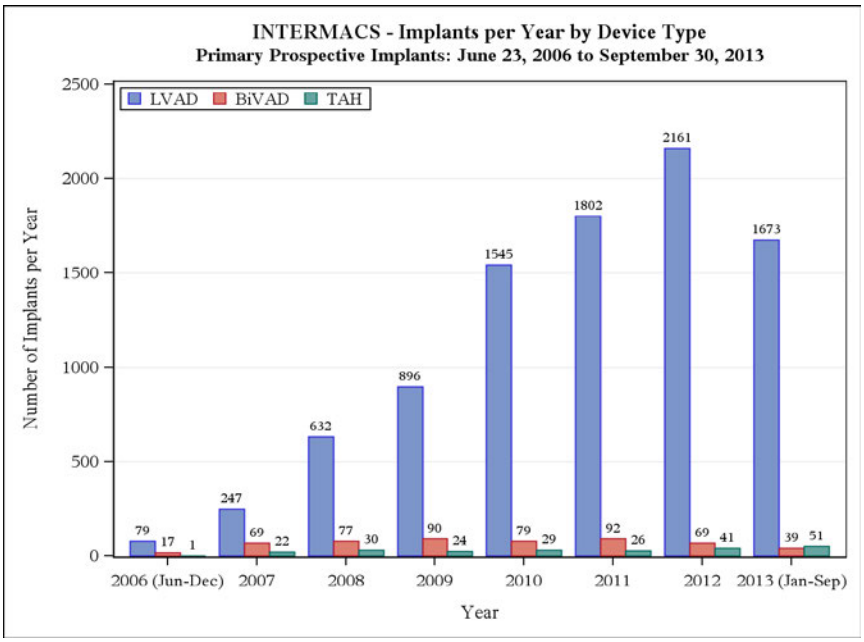
1.1. Heart Transplantation and Current Clinical Challenges:

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 U.S.[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[7] 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[8] *(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 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 (Figure 1). 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.

Figure 1: Source Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS); Quarterly Statistical Report, Q3, 2013.



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.

Figure 2: U.S. National Heart Transplant Waiting List Dynamics 2009-2011. Source: OPTN 2011/Scientific Registry of Transplant Recipients (SRTR) 2011 Annual Report: Transplant data 2011.

	2009	2010	2011	
Patients at start of year	2,409	2,668	2,867	
Patients added during year	2,890	2,916	2,783	
Patients removed during year	2,625	2,710	2,837	
Patients at end of year	2,674	2,874	2,813	
Removal reason				
Deceased donor transplant	1,840	1,965	1,931	
Patient died	435	400	441	~ 16%
Patient refused transplant	14	12	18	
Improved, tx not needed	193	164	166	
Too sick to transplant	55	61	92	~ 10%
Other	88	108	189	

1.2. Unutilized Donor Hearts

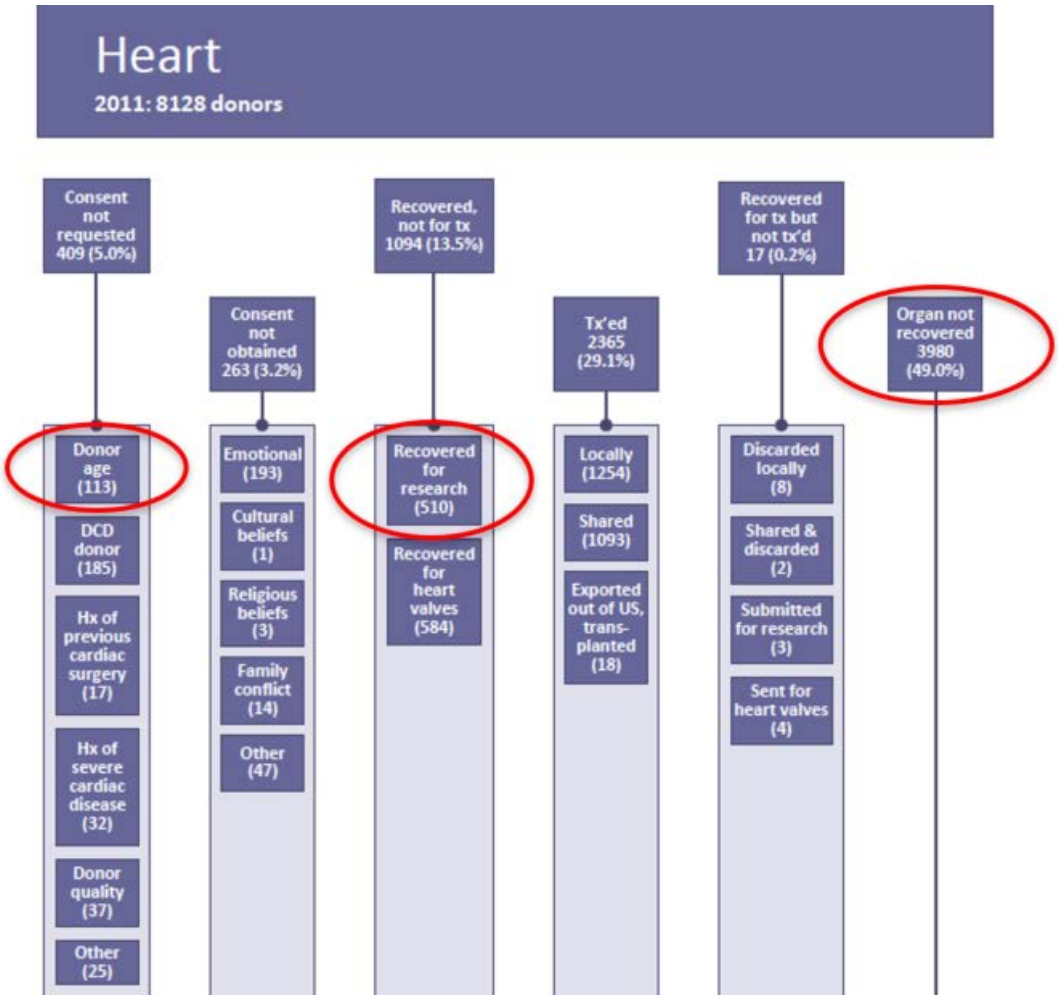
Below is the published data from the Scientific Registry of Transplant Recipients (SRTR) 2011 National Repot on the annual number of unutilized or non-recovered donor hearts in the U.S., and the clinical reasons for non-recovery. In 2011, there were 4,603 consented, donor hearts that

were not utilized in the U.S.; the same year only 1,931 patients underwent heart transplantation.[1] As shown in the table, the vast majority of reasons for not utilizing the donor hearts result from the existing limitations of cold storage.

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.

Figure 3: Heart Statistics



[1] OPTN 2011/Scientific Registry of Transplant Recipients (SRTR) 2011 Annual Report: Transplant data 2011. http://srtr.transplant.hrsa.gov/annual_reports/2010/318_ord.htm (last accessed Jan, 2013) http://srtr.transplant.hrsa.gov/annual_reports/2010/315_ord.htm?o=5&g=4&c=11

1.3. Potential Clinical Solutions to Overcome Limitation in Donor Heart Utilization

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.[10]

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[9] 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 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.

1.4. Summary of Prior Testing and Investigations

1.4.1. OCS™ Heart Engineering Testing

The OCS™ Heart device is CE marked and has undergone extensive preclinical testing to demonstrate its safety, effectiveness, and readiness for clinical use. The Heart Perfusion Set has also been evaluated and tested in accordance with ISO-10993 "Biological Evaluation of Medical Devices," including evaluations for acute toxicity, irritation, sensitization, cytotoxicity, hemolysis, genotoxicity and pyrogenicity. These test results demonstrated that the device and its materials are biocompatible and suitable for their intended use. The Heart Perfusion Set will be provided sterile using validated methods, and is appropriately packaged to maintain sterility. The OCS™ has also undergone extensive preclinical bench testing for: electrical safety, electromagnetic compatibility, and validation and verification testing (including validation of the device software). All tests and results have demonstrated that the OCS™ meets its expected performance specifications and is safe and suitable for clinical use.

1.4.2. OCS™ Heart Clinical Testing for Standard Routine Hearts

To-date the OCS™ Heart technology has been used to transplant > 100 human hearts worldwide from standard donors with good clinical results. The OCS™ PROCEED II pivotal trial has demonstrated the safety and effectiveness of OCS™ Heart technology to preserve standard donor hearts in a large multi-center, international trial that compared donor hearts preserved on OCS™ vs. cold storage.

1.4.3. OCS™ Heart Clinical Testing for Non-standard Donor Hearts

To-date the OCS™ Heart technology has been used internationally (UK, Germany and Australia) to preserve, assess and successfully transplant 50+ patients from donor hearts that otherwise may have been not transplanted using cold storage due to:

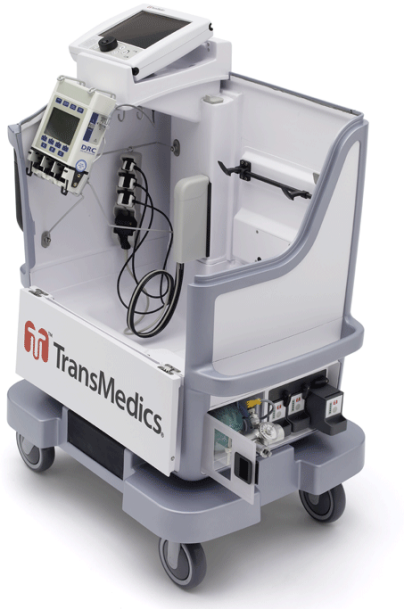
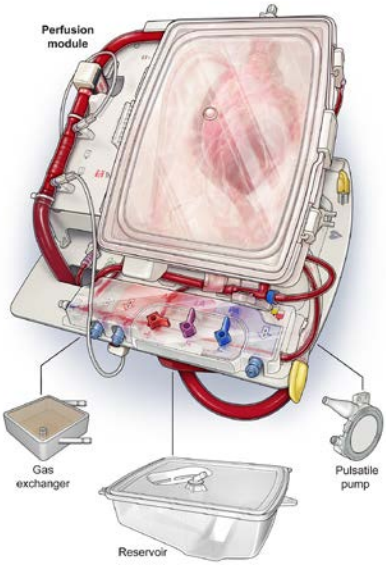
- Prolonged expected cross clamp time
- Left ventricular hypertrophy
- Questionable heart function in lieu of the suboptimal environment of brain death
- Social history of donor.

2. DEVICE DESCRIPTION

The OCS™ Heart System is an integrated portable platform designed to maintain donor hearts in a near physiologic, normothermic perfusion state. The OCS™ Heart System consists of:

- **The Portable Console & Monitor:** This is a compact electromechanical device that contains an integrated pulsatile perfusion pump, batteries, blood warmer, pressure, flow and saturation meters. In addition, it has an integrated wireless monitor that allows the clinical operator to control and display critical perfusion parameters of the preserved donor hearts.
- **OCS™ Heart Perfusion Set:** The HPS consists of the Heart Perfusion Module (HPM) and HPS Accessories. The HPM is a sterile, biocompatible perfusion module that maintains the organ's physiologic environment and has embedded sensors to optimize and monitor the heart perfusion parameters. In addition, the perfusion module enables perfusate sampling in order to monitor the heart's metabolic condition using standard blood gas and Lactate analyzers. The HPS Accessories are sterile, disposable accessories necessary to instrument the heart and manage the perfusate.
- **OCS™ Heart Solution:** This is a balanced nutrient physiologic solution used to supplement the donor blood perfusate with electrolytes, substrates and critical hormones that are depleted in the brain-dead donor body.

Figure 4: OCS™ Heart System Components

		
OCS™ Heart Console	**OCS™ Heart Perfusion Module (HPM)**	**OCS™ Heart Solution**

3. TRIAL OBJECTIVES

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 from one or more of the following characteristics:

- 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 age 45-55 years old with no coronary catheterization data; or
  - Donor age ≥ 55 years old; or
  - Left ventricular septal or posterior wall thickness of >12 ≤16 mm; or
  - Reported down time of ≥ 20 min, with stable hemodynamics at time of final assessment; or
  - Left heart ejection fraction (EF) ≥ 40 ≤ 50%; or
  - Donor angiogram with luminal irregularities with no significant CAD
  - History of Carbon monoxide poisoning with good cardiac function at time of donor assessment
  - Social history of alcoholism with good cardiac function at time of donor assessment; or

- History of diabetes combined with negative coronary angiogram for coronary artery disease (CAD).

3.1. Type of Trial

A prospective, pivotal, international single-arm trial of donor hearts and donor heart transplant recipients.

The proposed clinical trial seeks to evaluate the safety and effectiveness of the OCS™ Heart for donor hearts that today may not be transplanted due to the limitations associated with cold storage technique due to the impact of ischemia injury. As such, it is not possible to incorporate a concurrent control group. Thus, a single-arm trial of the OCS™ Heart is appropriate to evaluate this new use.

3.2. Trial Size and Subject Follow-up

This trial will be conducted at no more than 20 institutions, in the U.S. and world-wide (Europe, Australia and Canada) and will include up to 75 transplanted heart recipients. The number of subjects was determined as described in the statistical analysis section of this Investigational Plan/Protocol. Subjects will be followed for up to 12 months from the date of transplantation. The summary of the follow-up is in Appendix 3:

- All subjects will be followed from transplant to discharge
- 30-Day patient and graft survival will be documented on day-30 post-transplant eCRF.
- 6 and 12 months patient follow-up per Appendix 3.

4. TRIAL ENDPOINTS

4.1. Primary Effectiveness Endpoint

A composite endpoint of patient survival at Day-30 post-transplant and absence of severe heart primary graft dysfunction (PGD) (left or right ventricle)) in the first 24 hours post-transplantation.

4.2. Secondary Endpoints

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

4.3. Safety Endpoint

Incidence of heart graft-related Serious Adverse Events (SAEs) in the first 30 days post heart transplantation, defined as:

- Moderate or Severe Primary heart graft dysfunction (PGD) (left or right ventricles) (not including rejection or cardiac tamponade). Please see Appendix 2 for detailed definition of LV and RV PGD according to ISHLT consensus manuscript. Primary graft failure requiring re-transplantation

5. TRIAL POPULATION

The trial will include 55 heart transplant recipients, at up to 20 investigational sites in the U.S. and world-wide (Europe, Australia, and Canada).

5.1. Donor Eligibility Criteria

5.1.1. Donor Inclusion Criteria

Donor hearts are required to meet at least one of the following inclusion criteria:

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

5.1.2. Donor Exclusion Criteria

Donor hearts will be excluded if they meet any of the following criteria:

- Angiogram proven CAD with > 50% stenosis; or
- Cardiogenic shock or myocardial infarction; or
- Sustained terminal EF of < 40%; or
- Significant valve disease except for competent bicuspid aortic valve.

5.2. Recipient Eligibility Criteria

5.2.1. Recipient Inclusion Criteria

Recipients are required to meet all the following criteria on the day of transplant:

- Registered primary heart transplant candidate
- Age ≥ 18
- Signed: 1) written informed consent document and 2) authorization to use and disclose protected health information.

5.2.2. Recipient Exclusion Criteria

Recipients will be excluded if they meet any of the following criteria on the day of transplant:

- Prior solid organ or bone marrow transplant
- Chronic use of hemodialysis or diagnosis of chronic renal insufficiency
- Multi-organ transplant.

6. PRE-OPERATIVE TRIAL PROCEDURES

6.1. Subject Identification

All patients on the transplant waiting list who are being treated by trial investigators will be identified. Those patients who initially appear eligible for the trial will have the trial thoroughly explained to them, be invited to participate, and will be asked to sign an informed consent for participation in the trial prior to treatment. When a matching donor heart becomes available, the inclusion and exclusion criteria will be re-verified. When a final decision is made at the recipient site to transplant the heart, the recipient will be assigned a subject identification number.

6.2. Recipient Day of Transplant Assessment

The purpose is to conduct a final assessment of whether the potential consented recipient still meets the eligibility criteria. The following information will be verified and recorded on the day of transplant:

- **Eligibility*:*** Investigator will review and confirm that the potential consented recipient continues to meet all inclusion criteria and no exclusion criteria.
- **Demographics/Characteristics:**
  - Date of birth or Age
  - Gender, body mass index
  - Race and Ethnicity
  - Blood type and RH factor
  - Date of listing on the national heart transplant waiting list

  - Date of consent to the EXPAND Trial
  - Recipient ID
  - Recipient allocation urgency status
- **Recipient Risk Factors & Medical History:**
  - Indication for transplantation: The primary etiology of heart failure will be recorded
  - Presence of Circulatory Mechanical Support (LVAD, RVAD or total artificial heart) will be recorded. Type, brand, and date of insertion will be recorded
  - Panel reactive antibody %
  - Use of mechanical ventilation prior to transplantation
  - History of diabetes and type of treatment (insulin vs. oral hypoglycemic agents)

6.3. Donor Screening and Acceptance

Using the inclusion and exclusion criteria, the investigator or a member of her/his transplant team will evaluate the donor and the quality and suitability of the hearts for the trial. The following evaluations will be conducted and recorded:

- Organ Donor Identification Number and Type of Registry (e.g., UNOS ID, Eurotransplant ID)
- **Demographics:** Age, Date of birth (if available), gender, race, and ethnicity
- **Donor Characteristics:** Blood type & RH factor, body mass index
- **Donor's Cause of Death:**
  - Cause of death and date and time of pronouncement of brain death
  - Documented cardiac arrest witnessed or not and estimated down time
  - History of chest trauma and any evidence of sternum or rib fractures
- **Medical History:**
  - Active infection, positive serology for CMV, HIV, Hepatitis B or C, malignant tumors, and heart disease
  - History of diabetes
- **Social History:**
  - History of drug abuse or cocaine
  - Smoking
- **Donor Heart assessment:** The donor heart will be assessed prior to procurement and acceptance using the following methods:
  - **Angiogram findings (if available):** Evaluated for any potential pathology (e.g., coronary artery disease).

  - **ECHO findings (if available):** EF, wall motion, LV septum and wall thickness, and any valvular abnormalities.
  - **Final inspection and palpation prior to acceptance in the chest:** The donor heart will be evaluated for any contusions or any gross abnormalities.
- **Eligibility:** The donor will be evaluated to document whether the eligibility criteria are met. All eligibility criteria or clinical reasons for not accepting a donor heart at final assessment before retrieval will be recorded.

6.4. Donor Heart Retrieval and OCS™ Preservation and Assessment

After final evaluation of the donor heart in donor's chest and upon acceptance into the trial, the investigators will retrieve and preserve the donor heart according to the following protocol:

- **Initial Heart Flush in Donor Body:** all donor hearts will be arrested using 750-1000 ml of cold Del Nido heart arrest and flush solution OR identical chemical formulation (see below) flush via the aortic root according to standard retrieval procedure.

Del Nido Solution Formulation	Concentration
Base Solution 1 Liter	**Components (mmol/L)**
Na	140
Cl	98
K	5
Mg	3
Acetate	27
Gluconate	23
pH	7.4 (6.5-8)
Additives	**(ml/L base solution)**
KCL 2mEq/L	13
NaHCO3 1mEq/ml	13
MgSO4 50% - 0.5 g/ml	4
Lidocaine 1%	13
Mannitol 20%	16

- **OCS™ Heart Perfusion:** The OCS™ Heart system will be primed using:
  - 1.2-1.5 L of donor blood
  - 100-300 ml of 25% albumin solution
  - 300-500 ml of OCS™ Heart priming solution
  - Hearts preserved on the OCS™ Heart should be maintained according to the OCS™ Heart Instructions for use (IFU).

- **Lactate Level and other chemistries sampling scheme**: The organ retrieval team will collect samples from the donor and from the arterial and venous ports of the device and measure lactate levels using a standard blood gas analyzer according to the following protocol:
  - One blood sample will be collected from the donor prior to cross clamp (Donor Baseline Sample)
  - One blood sample will be collected after the donor's blood is added to the OCS™ circuit and prior to instrumentation of the donor's heart (Pre-instrumentation Sample).
  - One arterial and one venous sample will be collected within 10-20 minutes of perfusing the heart on the OCS™ Heart device.
  - At least, one additional arterial and venous sample will be collected before leaving the donor site.
  - Samples will continue to be collected from the device at approximately hourly intervals and after any active CF adjustment or any other adjustments.
- **The OCS™ Heart Preservation Parameters:** The OCS™ device parameters should be maintained within the following ranges after stabilization of the organ
  - Aortic Pressure (mean AOP): 40-100 mmHg
  - Coronary Flow (CF): 400-900 ml/min
  - Perfusate Temperature (Temp): 34^{o}C
  - Circulating total Lactate (Lact): < 5 mmol/L

  The ranges above represent the optimum perfusion values for the majority of the organs previous maintained on the OCS™ Heart System. However, the user may modify these parameters to achieve adequate preservation conditions for an individual organ.
- **OCS™ Device Malfunction(s):** will be recorded.
- **Final Heart Cooling and Flush Arrest on OCS™:** All donor hearts on OCS™ will be cooled down gradually to perfusate Temp. of 10-14°C using standard water cooler, followed by cold flush using 1 L of cold Del Nido arrest and flush solution OR identical chemical formulation (see above) flush according to the following protocol:
  - Use standard clinical cardiopulmonary bypass water heater-cooler device (for example Stöckert Heater-Cooler System 3T, Maquet HCU 30, or equivalent device) to perform the cool down protocol.
  - Set the water temperature of the water Heater-Cooler device to 34°C (similar to OCS™ Heart temperature).
  - Once at 34°C, connect the water Heater-Cooler water lines to the OCS™ Heart oxygenator water lines and start circulation.
  - Set the OCS™ heater temperature to Off.

  - Immediately lower the water Heater-Cooler device temperature by up-to 10°C lower than OCS™ temperature (for example, if OCS™ temp is 34, the water Heater-Cooler should be at 24°C) and reduce OCS™ pump flow by 100 mL/minute.
  - As the temperature displayed on the OCS™ Monitor approaches the Heater-Cooler water temperature set point (within 1-2°C), lower the Heater-Cooler water temperature by up to 10°C and reduce OCS™ pump flow by 100 mL/minute to allow the perfusate & organ to continue cooling.
  - Repeat this process until the desired target perfusate temperature (10-14°C is achieved, as displayed on the OCS™ Monitor.
  - Connect the cold cardioplegia bag to the aortic root port as per the OCS™ IFU.
  - Start administering the cold arrest & flush solution to the aortic root.
  - Turn off the OCS™ pump as per the OCS™ IFU.
- **Myocardial Protection of Donor Heart During Re-implantation:** Adequate myocardial protection:
  - Intermittent doses of antegrade (Aortic root) blood based cardioplegia every 20-30 minutes. Venting of the LA to avoid heart rewarming.
  - Reperfusion for at least 30 minutes prior to weaning from cardiopulmonary bypass.
- **Donor Retrieval Details:** The following information will be collected at time of heart retrieval
  - Date and time of cross clamp of donor aorta.
  - Need for external pacing will be recorded.
- **OCS™ Parameters and Enabled Measurements:** The following OCS™ Heart perfusion parameters and heart metabolic conditions will be recorded:
  - AOP
  - CF

  (AOP and CF are system data collected by the device during the preservation run and uploaded directly into the database)
  - Lactate level

6.5. Donor Heart Acceptance for Transplantation

- To maximize safety to potential recipients, the surgical procedure should not be initiated on the recipient until the donor heart has been clinically accepted by the transplanting surgeon/physician based on the below acceptance criteria.
- All donor hearts preserved on OCS™ Heart must meet the following clinical criteria for transplantation at final assessment on OCS™ Heart (Final Sample):

  - Final total arterial circulating OCS™ Heart perfusate Lact. Level < 5 mmol/L with stable lactate trend.
  - Stable CF, AOP trends within above ranges (certain expanded criteria organs, i.e., LVH hearts, may require higher CF and/or AOP to achieve adequate perfusion).
- Any decision to turn down hearts after the hearts have been retrieved, preserved and assessed on OCS™ Heart should be done with notification to the Site PI and the donor heart must be examined by the transplant center's qualified cardiac transplant pathologist and a central core lab for further assessment to evaluate any inherent cardiac pathology that was not diagnosed at retrieval of the donor heart.

7. TRANSPLANT, IMMEDIATE POST-OPERATIVE AND LONG-TERM FOLLOW-UP

7.1. Transplant Details

The following information concerning the transplant procedure will be collected:

- The organ recipient unique post-transplant patient identifier
- Total cross clamp duration in minutes (from donor cross-clamp application to removal of cross-clamp in the recipient)
- Post-OCS™ cold ischemia time (time from heart flush on OCS™ until aortic cross-clamp removal in the recipient)
- Any surgical complications encountered during surgery

7.2. Post-Transplant Functional Assessments Day 0 – Day 30

- Heart Primary Graft Dysfunction (PGD) Surveillance in the first 24 hours (see Appendix 1):
  - **Initial use of Mechanical Circulatory Support:** The use of ECMO, intra-aortic balloon, LVAD, RVAD, or bi-VAD will be recorded
  - **Inotropic Support for first 72 hours:** The following inotropic medication doses will be collected at ICU admission T0, T12, T24, T48, and T72 hours after ICU admission post-heart transplantation:
    - *Dopamine – mcg/kg/min*
    - *Dobutamine – mcg/kg/min*
    - *Amrinone – mcg/kg/min*
    - *Milrinone – mcg/kg/min*
    - Epinephrine – *mcg/kg/min*
    - Norepinephrine – *mcg/kg/min*
  - Right Heart Catheter Data between at ICU admission T0, T12, T24, T48 and T72 hours after ICU admission post-heart transplantation (if applicable):
    - Pulmonary Artery Pressures (PAP)
    - Pulmonary Capillary Wedge Pressure (PCWP)

  - Cardiac index (CI)
  - Right Atrial Pressure (RAP)

- **Initial use of Mechanical Respiratory Support:** Duration of initial post-transplant invasive ventilator support will be recorded from the time of initial admission to ICU post-heart transplant until extubation.
- **Initial Post-Transplant ICU Stay:** Intensive care unit (ICU) admission time, and date and time when clinical order for ICU discharge is written.
- **Immunosuppression Medications:** The type of immunosuppression medication and dose will be recorded at day 7 and at time of discharge from the hospital. Immunosuppression induction will be recorded if applicable.
- **Trans-thoracic echocardiogram results prior to Discharge will be recorded:**
  - Ejection Fraction (EF%)
  - Wall motion assessment
  - LV Septal and posterior wall thickness
  - Any valve abnormalities
- **Patient and Graft Survival at Day 30:** Patient and graft survival will be assessed on day 30 post-transplant.
- **Adverse Events:** All heart graft-related serious adverse events and any heart graft-related adverse events will be followed and documented until the investigator designates the event to be either resolved or its effect on the patient's condition stabilized.
- **Medications:** Medications used to treat all serious heart graft-related adverse event (SAE)-related will be recorded in the trial electronic database until the SAE is resolved.

These follow-ups will be attempted within ± 3 days of the designated periods expect for the PGD Surveillance in the first 24 hours which must be collected at the designated times. The evaluations may be conducted over several days.

7.3. Long-Term Follow-up: 6 and 12 months

Follow-up data collection will be conducted at approximately 6 and 12 months post-transplant.

- **6-month Follow-Up:** At approximately 6 months post-transplant, the patient will be evaluated at an office visit if this is the institution's standard of care, and, if not, by phone contact by the site. The patient's medical record may be reviewed to confirm patient's answers. This follow-up will collect information on:
  - Patient and graft survival;
  - Whether the patient was re-hospitalized after initial discharge, and, if so, the primary reason for the hospitalization and the length of stay;
  - Information will also be collected on any diagnosis of cardiac dysfunction and, if so, the method of diagnosis and treatment.

The 6-month follow-up will be collected within ± 1 month of the designated period and will be recorded on the 6-month follow-up electronic form.

- **12-month Follow-Up:** At approximately 12 months post-transplant, the patient will be evaluated at an office visit if this is the institution's standard of care, and, if not, by phone contact by the site. The patient's medical record may be reviewed to confirm patient's answers. This follow-up will collect information on:
  - Patient and graft survival
  - Results of standard of care coronary angiogram and right heart catheterization will be collected
  - Any diagnosis of cardiac allograft vasculopathy and, if so, the method of diagnosis (e.g., IVUS, coronary angio).

  The 12-month follow-up will be collected within ± 1 month of the designated period and will be recorded on the 12-month follow-up electronic form.

8. EVALUATION OF ADVERSE EVENTS

8.1. Evaluation of Heart Graft-Related Adverse Events

Heart Graft-Related Adverse Events are those which have any untoward effect on the health or safety of the patient and that are related to the transplanted heart function (except for acute rejection or myocardial tamponade). Heart graft-related adverse events will be collected from the time a subject is transplanted with a heart preserved on OCS™ until the completion of the 30-day follow-up evaluation. A heart graft-related adverse event will be followed until resolution or stabilization of the event.

8.2. Serious Adverse Events (SAEs)

An adverse event will be classified as serious if it meets any of the following criteria:

- Results in, leads to, or contributes to, a death
- Is life-threatening
- Results in permanent disability or incapacity (i.e., permanent impairment of a body function or permanent damage to a body structure)
- Requires in-patient hospitalization or prolongs hospitalization
- Necessitates medical or surgical intervention to preclude a permanent disability or incapacity
- Results in fetal distress, fetal death or a congenital anomaly/birth defect.

All heart graft-related SAEs will be followed until their resolution.

8.3. Anticipated and Unanticipated Adverse Events

The investigator will assess each adverse event for whether it is anticipated or unanticipated. An unanticipated adverse event is defined as any adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with, a device if that effect, problem or

death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the safety, or welfare of subjects.

Adverse events are associated with heart transplant procedures and have been documented within the first 30 days after heart transplant and are, therefore, anticipated. The list of events includes, but is not limited to:

- Acute rejection
- Atrial and ventricular arrhythmias
- Bleeding (major)
- Hemodynamic instability
- Death
- Fever
- Primary Graft Dysfunction
- Respiratory failure
- Graft failure
- Sepsis
- Renal dysfunction
- Hyperammonaemia
- Malignancy (post-transplant lymphoproliferative disorder (PTLD)
- Multiple organ failure
- Myocardial infarction
- Neurological dysfunction
- Hepatic dysfunction
- Diabetes due to steroid and anti-rejection medications
- Gall stones
- Pancreatitis
- Peptic ulceration
- Gastritis
- Gastro esophageal reflux disease (GERD)
- Aspiration
- Cardiac tamponade
- Pneumo-mediastinum
- Pneumothorax
- Hemothorax
- Pleural bleeding
- Pleural effusion
- Venous thromboembolism (deep venous thrombosis [DVT])
- Pulmonary embolism (PE)
- Sternal wound dehiscence
- Organ deemed not transplantable after retrieval
- Stroke
- Psychosis
- Cerebrovascular accident
- Peripheral vascular clotting or occlusion due insertion of mechanical support

- Limb gangrene due to vascular occlusion due insertion of mechanical support
- Use of mechanical circulatory support
- Coagulopathy
- Hyperacute rejection
- Anastomic site complications; narrowing, bleeding or occlusion
- Delayed sternal wound closure due to compromised cardiac function or excessive bleeding or both
- Bowel thromboembolic complications and gangrene
- Protamine and other anti-heparin medication reaction
- Heparin induced thrombocytopenia

8.4. Unanticipated Adverse Device Effect (UADE)

An UADE means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified or encountered before at least once in standard clinical practice, in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

8.5. Recording and Reporting of Adverse Event

All heart graft-related adverse events and serious adverse events are to be recorded on the electronic case report forms until post-transplant day 30. The description of the adverse event will include: the date of onset, duration, severity, seriousness, the relationship of the event to the trial treatment, anticipated or not, and any treatment required. All serious adverse events occurring during the course of the first 30 days post-transplant will be reported to TransMedics, Inc., as well as documented on the appropriate electronic case report form(s). For all SAEs, the investigator is required to supply any additional data that may be deemed necessary by the Sponsor. Additionally, any serious adverse events (SAE) and unanticipated adverse device effects (UADE) should be reported to TransMedics, Inc., preferably within 48 hours of the time the investigator learns of the event, but in no case later than 5 working days. Heart graft-related AEs will be recorded up to the 30-day follow-up or through hospital discharge if longer than 30 days. For any particular patient, the Independent Medical Monitor if required to protect patient safety may specify a different follow-up period. The Sponsor is responsible for the classification and reporting of heart graft-related adverse events to the appropriate regulatory authorities, and for the on-going safety evaluation of the trial in accordance with ISO 14155 and governing regulatory requirements.

8.6. Relationship of an Adverse Events to OCS™ Heart

The investigator will assess the relationship of the AE to the OCS™ Heart or to the standard of care, methods of preservation. The relationship will be assessed using the following categories:

- **Definitely Related:** There is a reasonable causal and temporal relationship between preservation with the OCS™ Heart and the adverse event.
- **Probably Related:** It is more likely than not that there is a reasonable causal relationship between preservation with the OCS™ Heart the adverse event.

- **Possibly Related:** There is a reasonable relationship with preservation with the OCS™ Heart and the adverse event, but the causal relationship is unclear or lacking.
- **Unlikely Related:** There is a temporal relationship with preservation with the OCS™ Heart and the adverse event, but there is not a reasonable causal relationship between the trial device and the event.
- **Unrelated:** There is no relationship between preservation with the OCS™ Heart and the adverse event.

8.7. Severity

The investigator will rate the severity of the adverse event using the following categories:

- **Mild:** The adverse event is transient and/or easily tolerated by the subject.
- **Moderate:** The adverse event causes the subject discomfort and interrupts the subject's usual activities.
- **Severe:** The adverse event causes considerable interference with the subject's usual activities.

8.8. Pre-Existing Conditions

Pre-existing diseases or conditions will not be reported as adverse events.

9. STATISTICAL METHODS

9.1. General

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.

In the case of missing outcome data, a multiple imputation model will be used to present a complete outcome analysis.

9.2. Analysis Populations

9.2.1. Transplanted Recipient Population

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

9.2.2. OCS™ Heart Population

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.

9.3. Analysis of Effectiveness Endpoints

9.3.1. Primary Effectiveness Endpoint

The primary hypothesis for this trial is that the true proportion of transplanted recipients with the composite of patient survival at Day 30 post-transplantation and absence of severe primary heart graft dysfunction (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: $\pi \leq 0.65$ and
H_1: $\pi > 0.65$

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

The primary effectiveness 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 at the 0.05 significance level will be performed to test the null hypothesis H_0. This endpoint will be analyzed using the transplanted recipient population.

9.3.2. Secondary Endpoints

The secondary endpoints for this trial are as follows:

- Patient survival at day-30 post-transplantation
- Incidence of severe primary heart graft dysfunction (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™ heart device.

Each secondary effectiveness endpoint will be summarized using counts and percentages and an exact 95% confidence interval for the true percentage based on the binomial distribution. The first two secondary effectiveness endpoints will be analyzed using the transplanted recipient population. The rate of donor hearts utilization that were successfully transplanted after preservation and assessment on the OCS™ heart device, will be analyzed using the OCS™ heart population.

9.4. Analysis of Safety

Safety will be analyzed principally by examination of the frequency of adverse events. In particular, the number of donor heart graft-related serious adverse events (SAEs) up to the 30-day follow-up after 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:

- Primary heart graft dysfunction (not including rejection or cardiac tamponade):
  - Use of ECMO, RVAD, LVAD, BiVAD or insertion of a new IABP for >12 hours post TX.
  - Use of ≥ 2 inotropic agents/vasopressors including high-dose epinephrine or norepinephrine for >7 days post heart TX.
  - Open chest post heart TX. due to compromised heart function
- Primary graft failure requiring re-transplantation

This endpoint will be summarized using descriptive statistics. A 95% confidence interval for the mean based on the t-distribution will be presented.

This endpoint will be analyzed based on the transplanted recipient population.

In addition, the numbers and percentages of subjects experiencing at least one heart graft-related AE, at least one (definitely or probably-related) device-related AE, at least one unanticipated AE, and at least one serious AE, and the number and percentage of deaths will all be tabulated. Also, the number of heart graft-related adverse events and the number and percentage of subjects experiencing adverse events will be tabulated by system organ class and preferred term using MedDRA. A similar analysis will be performed for serious AEs. AEs will also be tabulated at the event level by system organ class and preferred term and the relationship of the adverse event to the device using counts and percentages. Similar analyses will be performed by the severity of the adverse event.

9.5. Site Poolability

A site effect analysis will be conducted to assess the poolability of data. Sites with fewer than five subjects will be grouped into a larger Analysis Site. A chi-square test will be performed to evaluate site impact with a p-value of 0.15 defined as the threshold. If the p-value < 0.15 then analysis adjusting for site will be considered.

9.6. Sample Size Determination

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 heart graft dysfunction (PGD) (left or right ventricle) in the first 24 hours post-transplantation. The calculation assumed a one-sided exact binomial test, an alpha level of 0.05, a Performance Goal of 0.65, a true survival rate 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.

10. RISK ANALYSIS

This clinical trial has been designed to ensure that the benefits and knowledge gained from the trial outweigh the potential risks to the subjects. The subjects are adults undergoing primary heart transplants.

10.1. Potential Risks

The potential risks to subjects from participation in this clinical trial include the following:

- **Potential Risks Associated with Heart Transplant Procedures:** These risks include post-operative complications, such as graft failure, primary graft dysfunction, rejection, infection and other organs/systems complications, graft vessel disease (an expression of chronic rejection), infection, abnormal kidney function, diabetes, high level of cholesterol, high blood pressure, cancer and neurological complications.
- **The Potential Risk Associated with the Investigational Device:** As with any medical device, there is always a risk of extremely rare or previously unknown side effects developing from the treatment.
- **Potential Risk of Using a Donor Heart that is Unsuitable for Transplantation:** Regardless of the preservation system that is used, there is the risk that a patient can receive a heart that does not adequately function. This trial is designed to utilize hearts that would not be accepted for transplantation using cold storage preservation. There is the possibility that using such hearts may increase the risk of transplanting a heart that that does not function appropriately.

10.2. Manner in Which the Potential Risks Have Been Minimized

The Sponsor has relied upon a number of different means, including the device design, risk analysis and management process, preclinical testing, and the clinical protocol itself, to minimize the risks to subjects and to protect their safety and welfare. The sponsor has designed the device and conducted a risk analysis in accordance with ISO 14971 to minimize and mitigate the risks to subjects and users.

The Sponsor has conducted extensive preclinical testing of the OCS™ Heart to demonstrate its safety, effectiveness and readiness for clinical use. The OCS™ has undergone extensive preclinical and animal studies to demonstrate that the device performs as intended. These studies strongly indicate that the OCS™ Heart maintains heart viability by providing a controlled environment that simulates near-normal physiological conditions, and monitors its function. The Heart Perfusion Set has been tested for biocompatibility to minimize the risk of adverse tissue reactions. These test results demonstrate the device and its materials are biocompatible and suitable for their intended use. The OCS™ Heart Perfusion Solution used in this trial has been tested extensively in pre-clinical and clinical studies and has been CE marked since 2012. The Heart Perfusion Set and Perfusion solution are provided sterile and for single use to minimize the risk of infection. The OCS™ Heart has also undergone and continues to undergo extensive design verification and validation testing to optimize its performance and minimize the risks associated with its use. Preclinical studies demonstrate the device performs as intended and meets its performance specifications including the perfusion pump, the blood warmer, and other functions. The software has undergone and continues to undergo extensive testing to demonstrate it, and its safety functions and alarms, perform as intended.

This clinical protocol incorporates several procedures to minimize the risks to subjects and to ensure the benefits of the clinical trial outweigh its potential risks.

- The donor heart acceptance criteria after OCS™ Heart perfusion and assessment is designed based on clinically relevant markers for perfusion of donor hearts on OCS™ and clinical standards of accepting conventional donor hearts for transplantation.

Thus, the donor heart will be fully assessed based on the current standards of evaluating donor hearts before it is accepted for transplantation. The recipient will not be subjected to any surgical or medical procedures until the heart has been accepted for transplantation by the transplanting team

- Subjects will be monitored before, during and after the operative procedure to help ensure their safety. The investigators are members of transplant teams who have extensive experience with heart transplants and who will be trained to use the OCS™ Heart to further minimize risk.
- Subjects in the trial will undergo frequent visits and routine monitoring to help detect any abnormal changes and to provide appropriate treatment as necessary.
- The trial will be monitored to ensure the identification, documentation, and analysis of adverse events; and to ensure compliance with the protocol and procedures that are in place for conducting research to protect the safety and well-being of all subjects.

10.3. Potential Benefits

The low utilization of donor hearts has led to a severe shortage of donor hearts to meet the large and growing need for heart transplantation; the Scientific Registry for Transplant Recipients (SRTR) and Organ Procurement Transplant Network (OPTN) report a ~25% of the patients on the national waiting list have either died or they deteriorated in health status to be eligible for a heart transplant procedure.

The OCS™ Heart System's recruitment, preservation and assessment capabilities could potentially increase the rate of utilization of donor hearts that are currently wasted due to the limitations of cold storage techniques. This could dramatically improve the chances of waiting list recipients to receive a life-saving heart transplant and reduce waiting list time and mortality.

In addition, the OCS™ Heart's physiologic preservation of donor hearts could result in improved short and long-term post-transplant outcomes in the form of increased survival and lower graft dysfunction/rejection rates.

Furthermore, the OCS™ Heart's assessment capabilities of donor hearts ex-vivo, ensures that every donor heart studied must meet the current international standards for donor heart acceptance for transplantation, thus ensuring that the recipients are receiving acceptable hearts based on current standards and are not exposed to any further risk.

10.4. Risks Benefits Ratio

Based on the above, the benefits of using OCS™ Heart technology to recruit, preserve and assess donor hearts to ensure their suitability for heart transplantation outweigh any potential risks to the trial subjects.

11. DEVICE/SITE MANAGEMENT

11.1. Packaging and Labeling

The OCS™ Heart Perfusion Set and accessories and the Perfusion Solution will be supplied sterile and are intended and labeled for single use.

The OCS™ and its components will be clearly labeled as an investigational device according to 21 CFR 812.5. A copy of the IFU will be provided to each investigational site.

11.2. Storage

The investigational devices will be stored in a secure place. Access should be strictly limited to the investigators and their designees. Neither the investigators nor any designees may provide the investigational device to any subject not participating in this trial. Special storage instructions for the components are described below. The OCS™ Heart Perfusion Set should be stored at temperatures between -20°C and 50°C, and ambient humidity from 10-95%, no condensing.

Note: The OCS™ Heart Perfusion Set should be operated at ambient temperatures (10°C to 35°C), and ambient humidity (20%-90%).

11.3. Accountability

The investigator or designee will maintain an inventory record of investigational devices received, used for treatment, otherwise discarded, and returned to the Sponsor to assure FDA and the Sponsor that the investigational new device will not be dispensed to any person who is not a subject under the terms and conditions set forth in this protocol.

11.4. Device Complaints and Malfunctions

The investigator will inform the Sponsor of any complaints or malfunctions during the course of the trial. The Sponsor will investigate all device complaints and malfunctions.

12. REGULATORY/ETHICS

This clinical trial will be conducted in accordance with the requirements of the FDA Investigational Device Exemptions regulation (21 CFR Part 812), ISO Standard 14155, and in accordance with good clinical practices.

12.1. Institutional Review Boards (IRB) or Ethics Committee (EC)

Prior to initiation of any trial procedures, the protocol, informed consent and device labeling will be submitted to each site's IRB or EC for review and approval. In addition, any amendments to the protocol or informed consent form will be reviewed and approved (if necessary) by the IRB or EC. The Sponsor must receive a letter documenting the IRB's or EC's approval at the clinical site prior to the initiation of the trial at that particular site.

12.2. Informed Consent

Written informed consent will be obtained from all subjects before any trial-specific procedures are performed. Informed consent will be obtained and documented prior to initiation of any procedures that are performed solely for the purpose of the research trial.

Investigators have both an ethical and legal responsibility to ensure that each patient being considered for inclusion in this trial is given a full explanation of the protocol. This will be documented via a written informed consent form approved as part of the full trial approval granted by the Institutional Review Board (IRB) or Ethics Committee (EC) for the site. Each

informed consent form will include the elements required by 21 CFR Part 50. The investigator agrees to also obtain approval from the Sponsor and IRB/EC for any written informed consent form used in the trial.

The approved written informed consent form will be signed and dated by the subject and the individual obtaining the consent. The subject will be given a copy of the signed informed consent form. The original will be kept in the patient's file by the investigator.

A copy of the proposed draft Informed consent template is included as Appendix 4.

13. DATA COLLECTION/RECORDS/REPORTS

13.1. Investigator Records

Prior to participation in the investigation, the investigator will provide the following documentation to the Sponsor:

- Investigator Agreement, signed by the investigator and disclosure of any financial interest
- A copy of the primary investigator's curriculum vitae (CV), as well as copies of CVs for any co-investigators
- Written approval of the trial from the IRB or EC
- A copy of the approved informed consent document.

During the trial, investigators will be responsible for complete and accurate entry of data into the trial's database, and will be required to maintain on file the following accurate, complete and current records relating to this trial:

- All relevant correspondences and required reports that pertain to the trial
- Records of receipt, use or disposition of the investigational device, including the type and quantity of the device; the dates of receipt; the lot number; the names of all persons who received, used or disposed of each device; and why and how any units of the device have been returned to the Sponsor, repaired, or otherwise disposed
- Records of each subject's case history and exposure to the device
- Signed and dated consent forms
- Relevant observations, including records concerning adverse events, condition of each subject upon entering and results of diagnostic tests
- Protocol, and any amendments
- Subject recruiting materials
- Investigator curricula vitae.

The investigator will not dispose of any records relevant to this trial without (1) written permission from the Sponsor and (2) providing an opportunity for the Sponsor to collect such records. The investigator will take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial. Such documentation is subject to inspection by the Sponsor and regulatory authorities.

13.2. Investigator Reports

In accordance with the FDA reporting requirements, the investigators will be required to prepare and submit to the Sponsor the following complete, accurate, and timely reports on this investigation when necessary:

- The investigator will notify the Sponsor of a subject death occurring during the investigation as soon as possible, preferably within 24 hours of learning of the subject's death, but in no event later than 48 hours. The investigator will also notify the Sponsor immediately of a serious adverse event, preferably within 48 hours of learning of the serious adverse event, but in no event later than 5 working days.
- The investigator will notify the Sponsor of any unanticipated adverse device effects (UADE) preferably within 48 hours after the investigator first learns of the effect, but in no event later than 5 working days. The investigator will notify its IRB or EC of any unanticipated adverse device effects as soon as possible, but no later than 10 working days after the investigator first learns of the effect.
- The investigator will notify the Sponsor of the withdrawal of IRB or EC approval as soon as possible, but no later than 5 working days after the investigator first learns of the withdrawal
- The investigator will provide current progress reports to the Sponsor and reviewing IRB or EC at regular intervals but at least on an annual basis.
- The investigator will notify the Sponsor and the IRB or EC of any deviation from the investigational plan to protect the life and physical well-being of a subject in an emergency as soon as possible, but no later than 5 working days after the emergency occurred.
- The investigator will notify the Sponsor and IRB or EC that an informed consent was not obtained from a subject as soon as possible, but no later than 5 working days after such an occurrence.
- The investigator will provide a final summary report within 3 months after termination or completion of the trial to the IRB or EC. The site trial completion report may serve as the trial completion for the Sponsor
- The investigator will provide any other information upon the request of the IRB or EC, or the Sponsor.

13.3. Data Collection

During each subject assessment, an investigator participating in the trial will record progress notes to document all significant observations. In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes. For transmission to the Sponsor, information from the trial progress notes and other source documents will be promptly entered into the electronic database (eCRFs).

All data required by the trial protocol will be completely and accurately entered into the trial database by the investigator or his or her designate. Draft eCRFs are provided in Appendix 5.

13.4. Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, progress notes, electronic data, computer printouts, screening logs, and recorded data from automated instruments. All source documents pertaining to this trial will be maintained by the investigators and made available for inspection by authorized persons.

13.5. Archiving of Records

Essential trial documents must be maintained by the Investigator for at least 2 years after the last marketing approval by a regulatory body, as determined by the Sponsor. The documents should be retained for a longer period, however, if required by the applicable regulatory requirements. Records will be kept in a secure, dry location controlled by the institution.

13.6. Sponsor Records and Reports

The sponsor will conform to all records and reports requirements imposed by FDA's regulations.

14. CLINICAL MONITORING

14.1. Monitoring

The Sponsor has ethical, legal and scientific obligations to carefully follow this trial in a detailed and orderly manner in accordance with established research principles. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the Sponsor's monitors will visit the center during the trial in addition to maintaining frequent telephone and written communications. The following guidelines are provided to describe the Sponsor's procedures for monitoring the clinical studies. If the investigator is not complying with the signed Investigator Agreement, the protocol, or any condition of the trial, (e.g., incomplete data forms) the Sponsor has the right to terminate the investigator's participation in the trial. The Sponsor is responsible for selecting trial monitors qualified by training and experience to conduct monitoring of the trial and for ensuring the quality of the trial monitoring visits by the monitor. The Sponsor's general monitoring procedures for investigational studies are described below.

14.2. Pre-Trial Monitoring Procedures

14.2.1. Selection of Monitors

All monitors will be qualified by education, training, and experience.

14.2.2. Initiation Visit

A monitor will be responsible for determining and documenting that each investigator clearly understands and accepts the responsibilities and obligations incurred in conducting a clinical trial. The monitor will ensure, prior to trial initiation, that the investigator:

- Understands the requirements for a well-controlled trial
- Understands the nature of the clinical protocol

- Understands his/her reporting obligations
- Understands the requirements for device accountability
- Understands and accepts the obligations to obtain informed consent
- Understands and accepts the obligation to obtain IRB or EC review and approval of the clinical investigation before it is initiated and to ensure continuing review of the trial by the IRB or EC, and to keep the Sponsor informed of all IRB or EC actions concerning the trial
- Has adequate facilities, support staff, and access to an adequate number of suitable subjects to conduct the investigation
- Has the required documentation on file, including IRB or EC approval and a signed investigator agreement.

14.3. Periodic Monitoring Visits

Monitoring visits will be conducted as scheduled by the sponsor. The monitor should visit each site as needed to ensure the following:

- Facilities continue to be adequate and acceptable.
- Informed consent has been obtained.
- The protocol is being properly followed.
- The IRB or EC has approved or been notified of any protocol changes.
- Accurate, complete and current records are being maintained, and the information recorded and submitted to the Sponsor is representative of the subject's record and other supporting documentation.
- Accurate, complete and timely adverse event reports are being submitted to the Sponsor.
- The reason for a subject's withdrawal from the trial has been documented.
- Reports are being submitted to the IRB or EC and Sponsor.
- The appropriate staff is carrying out trial activities.

14.4. Frequency of Monitoring Visits

The frequency of monitoring visits will be determined on the basis of several factors, including the duration of the trial, number of subjects enrolled, number of investigators/sites, complexity of the trial, and number of outstanding issues from previous visits. All routine monitoring functions will be performed prior to the trial termination.

14.5. Trial Completion Visit

The trial termination visit may be combined with a monitoring visit. The following tasks will be completed at the last visit by the monitor.

- Ensure that all electronic forms have been completed.
- Ensure that any database queries have been resolved.

- Remind the investigator of the obligation to retain the records.

14.6. Reports of Monitoring Visits

Monitoring reports will be completed for all visits. Reports will include the date of the visit, list of trial personnel present, and a summary of the findings.

14.7. Additional Auditing

Regulatory authorities worldwide may also audit the investigator during or after the trial. The investigator will contact the Sponsor immediately if this occurs, and will fully cooperate with the audits conducted at a reasonable time in a reasonable manner.

14.8. Protocol Deviations

This trial will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of a subject requires a protocol deviation, based on the judgment of the investigator (or a responsible, appropriately trained professional designated by the investigator). If the deviation from the protocol is necessary to protect the life and physical well-being of a subject in an emergency, such protocol deviations will be reported to the Sponsor and the IRB or EC as soon as possible, but no later than 5 working days after the emergency occurred. In the event of a significant deviation from the protocol due to an accident or mistake, the investigator or designee will contact the Sponsor at the earliest possible time by telephone to discuss the deviation and its impact on the trial and subject continuation in the trial. These discussions will be documented by the investigator and the Sponsor, reviewed by the monitor, and documented on the Protocol Deviation eCRF.

14.9. Medical Monitor

The Sponsor will utilize an independent Medical Monitor to provide individual serious adverse event adjudication for the trial. It is anticipated that the Medical Monitor will meet with the Sponsor on a periodic basis, or as needed, depending on the rate of patient accrual. The primary responsibilities of the Medical Monitor are to:

- Review serious adverse events that occur over the course of the trial and the subsequent classification of these adverse events as related to the device
- Review donor and recipient treatment group eligibility issues.
- Evaluate possible protocol deviations.
- Provide oversight for issues affecting general patient welfare.
- Provide recommendations to extend the length of follow-up past 30 days post-transplant for a subject experiencing a serious adverse event.

14.10. Data Safety Monitoring Board & Stopping Rules

An independent Data Safety Monitoring Board (DSMB) will be established by the Sponsor to periodically assess the progress of the trial, the safety data and the primary efficacy and safety endpoints. The DSMB will make recommendations to the Sponsor regarding continuation, modification or termination of the clinical trial. The DSMB will review all data submitted to them by the Sponsor and may request additional information to assist in their decision process.

They will attend scheduled meetings and issue written minutes of their meetings; furthermore, the appointed Chair will be responsible for issuing final written recommendations.

The following stopping rule is to be used in the study:

> **Stopping Rule:** Let p denote the true proportion of recipients transplanted with an OCS-treated heart for whom the recipient does not survive until Day 30. Whenever a recipient dies within 30 days post-transplant, calculate a 97.5% lower confidence bound for p. Stop the study if this lower confidence bound exceeds 0.15 (15%).

Table 1 below shows the conditions under which the study would be stopped for a range of number of deaths (m) and a range of number of recipients (n). (The above stopping rule would, however, be applied to all combinations of number of deaths and number of recipients that were observed in the study.) The letter "S" in a cell indicates that the study would be stopped if this condition were met. If the letter "C" appears, the study would continue. A dash indicates an impossible condition, with m > n. One sees, for example, that the study would be stopped if there were 4 deaths out of the first 5 recipients or 5 deaths out the first 10 recipients.

Table 1: Conditions under which Study would be Stopped

n	M											
	1	2	3	4	5	6	7	8	9	10	11	12
5	C	C	C	S	S	-	-	-	-	-	-	-
10	C	C	C	C	S	S	S	S	S	S	-	-
20	C	C	C	C	C	C	S	S	S	S	S	S
30	C	C	C	C	C	C	C	C	C	S	S	S
40	C	C	C	C	C	C	C	C	C	C	C	S

TransMedics will be responsible for implementing the stopping rule.

14.11. Investigator Training

Device, protocol and electronic database training will be provided to all the participant investigators and support staff prior to patient enrollment in the trial. Device training will be conducted at the TransMedics clinical training facility or equivalent training facility. Protocol training will include a thorough review of this protocol. Electronic database training will consist of an explanation of the structure of the database, the data elements to be collected, simulated use of the database, error handling, and instructions regarding the handling of queries.

15. CONFIDENTIALITY

All information generated in this trial will be considered highly confidential and must not be disclosed to any persons not directly concerned with the trial without written prior permission from the Sponsor. Authorized regulatory officials and Sponsor personnel (or their representatives) will be allowed full access to inspect and copy the records. All investigational devices, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor. Subjects will be identified only by initials and unique subject numbers on the case report forms. If necessary,

their full names may be made known to the Sponsor, a regulatory agency, or other authorized officials.

16. AMENDMENT POLICY

The investigator will not make any changes to this protocol without prior written consent from the Sponsor and subsequent approval by the IRB or EC, except if the deviation from the protocol is necessary to protect the life and physical well-being of a subject in an emergency. Such protocol deviations will be reported to the Sponsor and the reviewing IRB or EC as soon as possible, but no later than 5 working days after the emergency occurred. Any permanent change to the protocol, whether it is an overall change or a change for specific trial center(s), will be handled as a protocol amendment. Any amendment to the protocol that appears indicated as the trial progresses will be fully discussed by the investigator(s) and the Sponsor. If agreement is reached regarding the need for an amendment, it will be written by the Sponsor. The written amendment will be submitted to the chairman of the IRB or EC responsible for reviewing amendments. Except for "administrative letters," investigators will await IRB or EC approval of protocol amendments before implementing the change(s). Administrative letters are defined to have no effect on the validity of the data or information resulting from the completion of the approved protocol, or the relationship of likely patient risk to benefit relied upon to approve the protocol; the scientific soundness of the investigational plan or protocol; and, the right, safety or welfare of the human subjects involved in the investigation. The Sponsor will notify the FDA of such changes in a 5-Day Notice. When, in the judgment of the IRB or EC, the investigators and/or the Sponsor, the amendment to the protocol substantially alters the trial design and/or increases the potential risk to the subject; such changes will be approved by the FDA and the IRB and EC.

17. REFERENCES

1. Hunt SA. Taking heart: Cardiac transplantation past, present, and future. N Engl J Med 2006; 355: 231–235.
2. Hunt SA, Haddad F. The changing face of heart transplantation. J Am Coll Cardiol 2008; 52: 587–598.
3. The Registry of the International Society for Heart and Lung Transplantation. Introduction to the 2012 annual reports: New leadership, same vision. J Heart Lung Transplant 2012; 31: 1045–1095.
4. OPTN 2011/Scientific Registry of Transplant Recipients (SRTR) 2011 Annual Report: Transplant data 2011.
5. Kobashigawa J, Zuckermann A, Macdonald P, et al. Report from a consensus conference on primary graft dysfunction after cardiac transplantation. J Heart Lung Transplant. 2014 Apr;33(4):327-40.
6. Iyer A, Kumarasinghe G, Hicks M, et al. Primary graft failure after heart transplantation. *J Transplant.* 2011:175768.
7. Parolari A, Rubini P, Cannata A, et al. **Endothelial damage during myocardial preservation and storage.** *Ann Thorac Surg*. 2002;73:682–690
8. Smith M. Physiologic changes during brain stem death-lessons for management of the organ donor. J Heart Lung Transplant. 2004 Sep;23(9S):S217-S222.

9. Hassanein W, Zellos L, et al. Continuous perfusion of donor hearts in the beating state extends preservation time and improves recovery of function. J Thorac Cardiovasc Surg. 1998 Nov;116(5): 821-30.
10. Van Raemdonck D, Neyrinck A, et al. Machine perfusion in organ transplantation: a tool for ex-vivo graft conditioning with mesenchymal stem cells? Cur Opinion transplant. 2013 Feb; 18(1): 24-33.

APPENDIX 1. INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION CONSENSUS ON HEART PRIMARY GRAFT DYSFUNCTION GRADING (PGD) SYSTEM

(Kobashigawa J, et al. 2014)

Table 5 Classification of Graft Dysfunction

1. Primary graft dysfunction (PGD):
   a. PGD-left ventricle (PGD-LV): Includes left and biventricular dysfunction.
   b. PGD-right ventricle (PGD-RV): Includes right ventricular dysfunction alone.
2. Secondary Graft Dysfunction: Occurs when there is a discernible cause for graft dysfunction (e.g., hyperacute rejection, pulmonary hypertension, known surgical complication).

Table 6 Definition of Severity Scale for Primary Graft Dysfunction (PGD)

1. **PGD-Left ventricle (PGD-LV):**	*Mild PGD–LV*: *One* of the following criteria must be met:	LVEF $\leq$ 40% by echocardiography, *or* Hemodynamics with RAP > 15 mm Hg, PCWP > 20 mm Hg, CI < 2.0 L/min/m^2 (lasting more than 1 hour) requiring low-dose inotropes
	Moderate PGD-LV: Must meet one criterion from I *and* another criterion from II:	I. *One* criteria from the following: Left ventricular ejection fraction $\leq$ 40%, *or* Hemodynamic compromise with RAP > 15 mm Hg, PCWP > 20 mm Hg, CI < 2.0 L/min/m^2, hypotension with MAP < 70 mm Hg (lasting more than 1 hour) II. *One* criteria from the following: i. High-dose inotropes—Inotrope score > 10[a] *or* ii. Newly placed IABP (regardless of inotropes)
	Severe PGD–LV	Dependence on left or biventricular mechanical support including ECMO, LVAD, BiVAD, or percutaneous LVAD. Excludes requirement for IABP.
2. PGD-right ventricle (PGD-RV):	Diagnosis requires either both i and ii, or iii alone:	i. Hemodynamics with RAP > 15 mm Hg, PCWP < 15 mm Hg, CI < 2.0 L/min/m^2 ii. TPG <15 mm Hg and/or pulmonary artery systolic pressure < 50 mm Hg, *or* iii. Need for RVAD

BiVAD, biventricular assist device; CI, cardiac index; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RVAD, right ventricular assist device; TPG, transpulmonary pressure gradient.

[a]Inotrope score = dopamine (×1) + dobutamine (×1) + amrinone (×1) + milrinone (×15) + epinephrine (×100) + norepinephrine (×100)[67] with each drug dosed in μg/kg/min.

APPENDIX 2. SAFETY PROFILE ENDPOINTS

The safety endpoint is the number of heart graft-related serious adverse events up-to the 30-day follow-up after 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 (see below):

1. **Moderate Left Ventricular Primary Graft Dysfunction PGD - Left Ventricle (Moderate PGD-LV):** Must meet one criterion from Section A **AND** another criterion from Section B below:

   A. One criteria from the following:

   – LVEF ≤ 40%

   OR

   – Hemodynamic compromise with RA>15, PCW>20, CI<2.0, hypotension with MAP<70mmHg (lasting more than 1 hour)

   B. One criteria from the following

   – High dose inotropes—Inotrope score ≥ 10*

   *Inotrope score: dopamine (×1) + dobutamine (×1) + amrinone (×1) + milrinone (×15) + epinephrine (×100) + norepinephrine (×100) [66]Each drug dosed in mcg/kg/min

   OR

   – Newly placed IABP (regardless of inotropes)

2. **Severe PGD - Left Ventricle (Severe PGD-LV)**

   A. Dependence on left or biventricular mechanical support including ECMO, LVAD, BiVAD or percutaneous LVAD. Excludes requirement for IABP.

3. **PGD- Right ventricle (PGD-RV) -** Diagnosis requires both (A and B) of the following criteria to be met:

   A. Hemodynamics with RA>15, PCWP<15, CI<2

   B. Transpulmonary gradient (TPG) ≤15 and/or pulmonary artery systolic pressure (PAS) <50mmHg.

   OR

   C. Need for RVAD.

APPENDIX 3. 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	Mo 6	Mo 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 AE's & SAE's	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.

APPENDIX 4. DRAFT PATIENT INFORMED CONSENT FORM TEMPLATE

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APPENDIX 5. DRAFT ELECTRONIC CASE REPORT FORMS

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