INVESTIGATIONAL PLAN/PROTOCOL

Clinical Trial to Evaluate the Safety and Effectiveness of The Portable Organ Care System (OCS™) Heart For Resuscitation, Preservation and Assessment of Hearts from Donors after Circulatory Death (DCD Heart Trial)

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CONFIDENTIAL – PROPRIETARY INFORMATION

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OCS™ DCD HEART SYNOPSIS

Protocol Title	Trial to Evaluate the Safety and Effectiveness of The Portable Organ Care System (OCS™) Heart for Resuscitating, Preserving and Assessing Hearts Donated after Circulatory Death (OCS™ Heart U.S. DCD Heart Trial)
Objectives	To evaluate the effectiveness of the OCS Heart System to resuscitate, preserve and assess hearts donated after circulatory death for transplantation to increase the pool of donor hearts available for transplantation.
Trial Design	A prospective, randomized and concurrent controlled, non-inferiority pivotal trial in which subjects who receive a DCD donor heart transplant will be compared to subjects who receive a standard criteria donor heart transplant (SOC1 and SOC2 - from both randomized and concurrent control groups), adjusting for differences in risk factors.
Trial Size	A maximum of 25 participating sites with 90 transplanted DCD heart recipients and 90 standard of care heart transplant recipients. Follow-up data for the SOC recipients will be obtained from UNOS/OPTN database for U.S. heart transplant recipients.
Screening and Treatment	Primary heart transplant candidates will be screened for trial eligibility. Every eligible candidate will be asked to participate. Subjects will be randomized into two groups: ***DCD Heart Possible*** and ***SOC Heart Only*****.** Subjects who are randomized into the ***SOC Heart Only*** group will have no possibility for a DCD Heart transplant. Subjects randomized into the ***DCD Heart Possible*** group have the possibility of receiving either a DCD heart preserved on OCS or an SOC donor heart, depending upon the donor match. In order to obtain enough subjects with DCD donor heart transplants, subjects will be randomized 3:1 to the ***DCD Heart Possible*** and ***SOC Heart Only*** arms, respectively. Follow-up survival data for transplanted subjects in ***the SOC Heart Transplanted Recipient (SOC1)*** group will be obtained from the UNOS/OPTN standard database for transplant recipients. Upon receiving a donor heart match and after confirmation of eligibility, SOC Heart transplanted recipients will have demographic information collected and will then exit the study and undergo standard heart transplantation according to the institution's standard of care. In the ***DCD Heart Possible*** arm, if a screened and eligible subject is matched with an SOC donor heart before an eligible DCD donor heart becomes available and is transplanted, these subjects will form a second ***SOC Heart Transplanted Recipient group (SOC2)***. Follow-up survival data for subjects in the ***SOC2*** group will be obtained from the UNOS/OPTN standard database for transplant recipients. Upon receiving a donor heart match and after confirmation of eligibility, SOC Heart transplanted recipients will have demographic information collected and will then exit the study and undergo standard heart transplantation according to the institution's standard of care. Data will be collected according to this protocol for subjects in the DCD Heart Possible arm who receive a DCD Heart match and are transplanted with the DCD heart as outlined in this protocol (***DCD Heart Transplanted Recipient group)***.
DCD Donor Heart Eligibility Criteria	**Inclusion** • Maastricht Category III DCD donor, defined as expected death after the withdrawal of life-supportive therapy (WLST) • Donor age 18-49 years old inclusive • Warm ischemic time (WIT) ≤ 30 mins, with warm ischemic time defined as: Time from when mean systolic blood pressure (SBP) is < 50 mmHg or peripheral saturation < 70% to aortic cross-clamp and administration of cold cardioplegia in the donor. **Exclusion** • Previous cardiac surgery; • Known coronary artery disease; • Cardiogenic shock or myocardial infarction; • Sustained terminal EF of ≤ 50%; or • Significant valve disease except for competent bicuspid aortic valve.
Standard Criteria (SOC) Donor Hearts	Standard criteria donor hearts will be screened and determined to be eligible for transplant according to the standard of care at each institution

Recipient Eligibility Criteria	**Inclusion** • Primary heart transplant candidates • Age ≥ 18 years old • Signed: (1) written informed consent document; (2) authorization to use and disclose protected health information; and (3) consent to TransMedics' use of recipients' UNOS/OPTN data and recipients' INTERMACS data. **Exclusion** • Prior solid organ or bone marrow transplant • Chronic use of hemodialysis or diagnosis of chronic renal insufficiency • Multi-organ transplant • Investigator unwilling to randomize to either arm.
DCD Donor Heart on OCS Transplant Criteria	**Accept for Transplantation** Donor hearts preserved on the OCS Heart System to be maintained within the following target ranges: • Stable or downward trending lactate after initial adjustments of the OCS Heart perfusion parameters to achieve adequate perfusion to the donor heart • Stability of OCS Heart perfusion parameters within range: ○ AOP 40-100 mmHg • Transplanting surgeon and/or heart failure cardiologist must clinically accept the OCS perfused donor heart for transplant. **Reject for Transplantation** • Transplanting surgeon and/or heart failure cardiologist clinically unsatisfied with donor heart condition/performance on the OCS Heart System at final evaluation • Unstable and rising arterial lactate despite maneuvers to optimize perfusion parameters. Note: Certain donor hearts may require perfusion with parameters outside of these guidance ranges. Acceptance for transplantation should be primarily based on an acceptable lactate trend.
Primary Endpoint	• A non-inferiority comparison of patient survival at 6 months post-transplant between recipients of DCD donor hearts preserved on the OCS Heart System and recipients of standard criteria donor hearts preserved using cold storage (***SOC1 + SOC2***), adjusting for risk factors.
Secondary Endpoint	• Utilization Rate, defined as the number of eligible DCD donor hearts that met the warm ischemic time limit above and were instrumented on the OCS Heart System that meet the acceptance criteria for transplantation after OCS Heart preservation divided by the total number of eligible DCD donor hearts that met the warm ischemic time limit above and were instrumented on the OCS Heart System.
Other Endpoints (Calculated for DCD Transplanted Recipients only)	• Patient and graft survival at 30 days post-transplant • Patient and graft survival at 30 days and initial hospital discharge, if later than 30 days • Severe heart primary graft dysfunction (PGD) (left or right ventricle) (not including rejection or cardiac tamponade) according to ISHLT consensus manuscript (as defined in Appendix 1 of this protocol) • Use of post-transplant mechanical circulatory support (LVAD, RVAD, BiVAD) for > 72 hours immediately post-transplant.
Safety Endpoint (Calculated for DCD Transplanted Recipients only)	The safety endpoint is defined as the incidence of heart graft-related Serious Adverse Events (HGRSAEs) in the first 30 days post-heart transplantation in the DCD Heart Transplanted Recipient Population, defined as the following adverse events (at most one per type): • Moderate or Severe heart PGD (left or right ventricle) (not including rejection or cardiac tamponade) according to ISHLT consensus manuscript (as defined in Appendix 1 of this protocol). • Primary graft failure requiring retransplantation This endpoint is calculated for the DCD Heart Recipient population only.
Other endpoints	• Patient survival at 1 year after transplant (collected post-approval); comparison of ***DCD Transplanted recipients*** and standard of care recipients (***SOC1 + SOC2***) through UNOS/OPTN database.

Follow-up	• All patients will be followed for 6 months pre-market. 1 year follow-up will be post-market.
Statistical Methods	The ***DCD Heart Transplanted Recipient Population*** will consist of all eligible recipients who are transplanted with an eligible DCD donor heart that met the warm ischemic time limit defined above, preserved on OCS and met the transplantability criteria. The analyses of all effectiveness and safety endpoints, except the utilization rate, will be based on the DCD Heart Transplanted Recipient Population. ***The OCS Heart Population*** will consist of all eligible donor hearts that met the warm ischemic time limit above and were instrumented on the OCS Heart System. The analysis of utilization rate will be based on the OCS Heart population. The ***SOC Heart Transplanted Recipient Population*** will consist of all recipients who received a standard criteria donor heart (***SOC1 + SOC2*** as defined in Section 6.4). The analyses of the primary endpoint and of patient survival at one year after transplant will be based on the DCD Heart Transplanted Recipient Population and the SOC Heart Transplanted Recipient Population. The analyses of: (1) patient and graft survival at 30 days post-transplant; (2) patient and graft survival at 30 days and at initial hospital discharge if longer than 30 days; (3) the use of post-transplant mechanical circulatory support (LVAD, RVAD, and BiVAD) for > 72 hours immediately post-transplant; (4) Severe heart PGD (left or right ventricle) (not including rejection or cardiac tamponade) according to ISHLT consensus manuscript (as defined in Appendix 1 of this protocol); and (5) HGRSAEs and SAEs will be based on the DCD Heart Transplanted Recipient Population. **Statistical Analysis** The primary endpoint is a comparison of survival at 6 months for DCD heart transplanted recipients and standard criteria heart transplanted recipients (SOC1 + SOC2 as defined in Section 6.4), adjusting for differences in risk factors. This is a non-inferiority study. **Risk Factors** We will adjust for the known donor and recipient risk factors for mortality shown in the list below[1]: Donor Variables: • Donor Age ≥ 55 years • Gender mismatch (female donor to male recipient). Recipient Variables: • Age ≥ 65 • LVAD, ECMO or IABP prior to transplant For continuous baseline characteristics, two-sided, two-sample t-tests will be used to test for a difference in means between treatment groups. For categorical baseline characteristics, the chi-square test will be used to test for a difference in proportions between treatment groups. We will adjust the analysis of the primary endpoint for any of these baseline characteristics for which there is a statistically significant difference (p-value < 0.15) between the treatment groups. The null and alternative hypotheses for the primary endpoint are as follows: H_0: $p_{SOC} - p_{DCD} \geq 0.20$ vs. H_1: $p_{SOC} - p_{DCD} < 0.20$

[1] Cardiac Donor Risk Factors Predictive of Short-Term Heart Transplant Recipient Mortality: An Analysis of the United Network for Organ Sharing Database. Trans Proc. 2015 Dec; 47(10): 2944-2951., Heart Transplant Survival based on Recipient and Donor Risk Scoring: A UNOS Database Analysis, ASAIO J., 2016; 62:297-301. Report from the American Society of Transplantation Conference on Donor Heart Selection in Adult Cardiac Transplantation in the United States. Am.J.Transplant, 2017; 17:2559-2566

where p_{DCD} and p_{SOC} represent the true survival proportions at 6 months for DCD and SOC heart transplant patients, respectively.

The analysis of this endpoint will be performed using a linear probability model, with the following terms in the model: (1) treatment; (2) all of the known donor and recipient risk factors listed previously; and (3) any of the potential risk factors listed above for which there is a statistically significant difference between treatment groups. The p-value for the test of the null hypothesis will be obtained based on a statistic for the difference (SOC - DCD) in least squares means (actually proportions rather than means) for each treatment minus the non-inferiority margin of 0.20 all divided by the standard error of the difference in the least squares means and assuming an approximate normal distribution. The test will be conducted at the 0.05 level of significance.

Secondary and Other Endpoints
Secondary Endpoint:
Utilization Rate, defined in Section 5.2

Other Endpoints:
DCD Heart Transplanted Recipients only:

- Patient and graft survival at 30 days post-transplant
- Patient and graft survival at 30 days post-transplant and at initial hospital discharge, if later than 30 days
- Severe heart PGD (left or right ventricle) (not including rejection or cardiac tamponade) according to ISHLT consensus manuscript (as defined in Appendix 1 of this protocol)
- Use of post-transplant mechanical circulatory support (LVAD, RVAD, BiVAD) for > 72 hours immediately post-transplant.

DCD Heart Transplanted Recipients and SOC Heart Transplanted Recipients:

- Patient survival at one year after transplant (collected post-approval and collected from UNOS for SOC Heart Transplanted Recipients).

Each endpoint will be summarized using counts and percentages and an exact (Clopper-Pearson) 95% confidence interval for the true percentage based on the binomial distribution. Patient survival at one year after transplant will be summarized for both the DCD Heart Transplanted Recipient and SOC Heart Transplanted (SOC1 + SOC2 as defined in Section 6.4) Recipient populations.

Comparisons of recipient demographics and baseline characteristics and of patient survival at 6 months will be performed for the following treatment groups (as defined in Section 6.4):

- SOC1 vs SOC2
- DCD Heart vs SOC1
- DCD Heart vs SOC2

Continuous demographic and baseline characteristics will be summarized by treatment group using descriptive statistics (mean, standard deviation, median, minimum, and maximum). Categorical demographic and baseline characteristics and patient survival at 6 months will be summarized by treatment group using counts and percentages. For continuous variables, comparisons of treatment groups will be performed using two-sided, two-sample t-tests. For categorical variables, comparisons will be performed using Fisher's Exact Test.

Safety (DCD Heart Transplanted Recipient Population Only)
Serious Adverse Events (SAEs) and Heart Graft-related Serious Adverse Events (HGRSAEs) will be collected within the first 30 days post-transplant and the mean number of HGRSAEs per subject will be summarized using descriptive statistics. HGRSAEs are defined as the following adverse events (at most one per type): Moderate or Severe heart PGD (left or right ventricle) (not including rejection or cardiac tamponade)

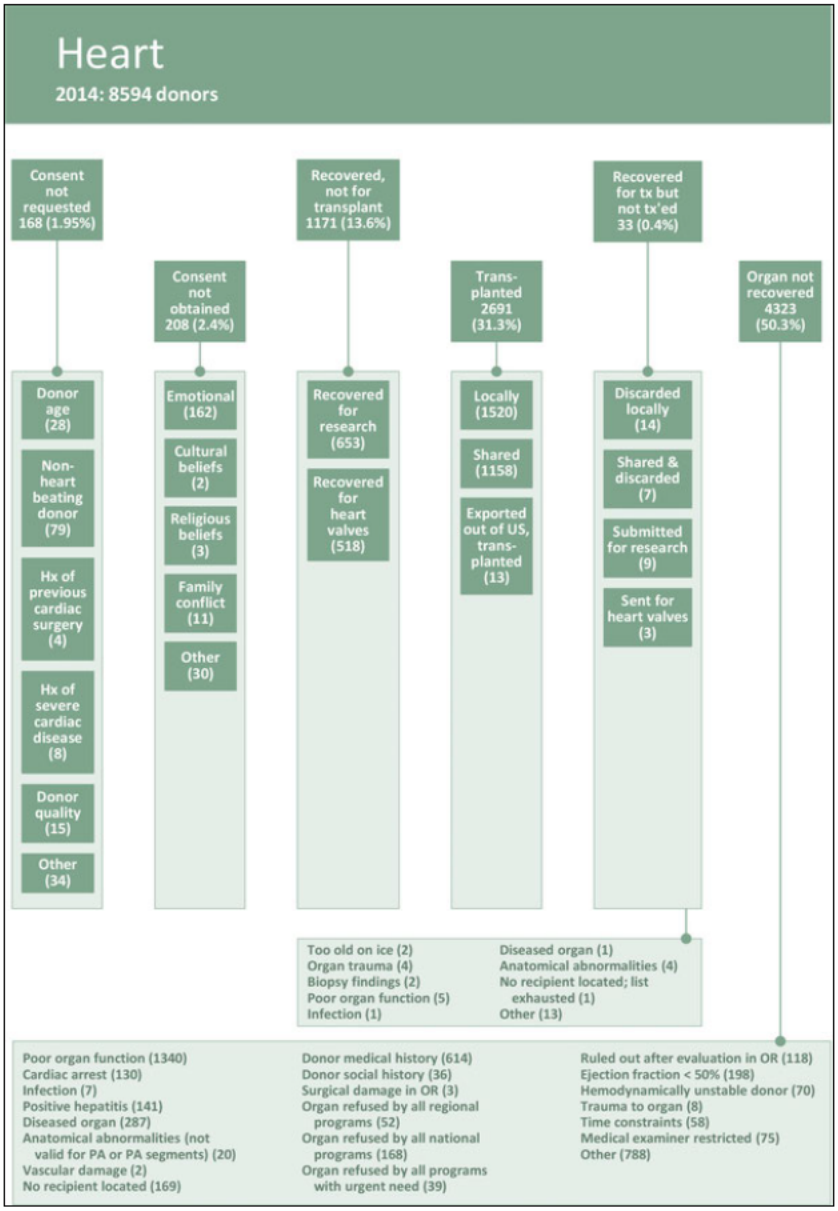
	according to ISHLT consensus manuscript (as defined in Appendix 1 of this protocol) and primary graft failure requiring retransplantation. SAEs and HGRSAEs will also be tabulated using counts and percentages alone and in regards to the relationship of the HGRSAE to the device, and the severity of the HGRSAE. **Sample Size Determination** We have assumed that transplantation of a DCD donor heart will occur at the same ratio as SOC heart transplants, despite the 3:1 randomization of ***DCD Heart Possible*** to ***SOC Heart Only***. The sample size calculations are based on the following specifications: • Non-inferiority study with comparison of DCD heart transplanted recipients to SOC heart transplanted recipients • Primary endpoint is patient survival at 6 months post-transplant • One-sided normal approximation test • Alpha = 0.05 • Power = 80% • Assume 1:1 occurrence of SOC heart transplants (SOC1 and SOC2) and DCD heart transplants • True SOC survival percentage = 93% • True DCD survival percentage = 85% • Non-inferiority margin = 20%. Based on these assumptions, a sample size of 84 DCD heart transplanted recipients and at least 84 SOC heart transplanted recipients will provide at least 80% power. This sample size was increased to 90 per group to reflect potential enrollment of subjects who are lost to follow-up, withdraw or do not meet eligibility criteria.
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:

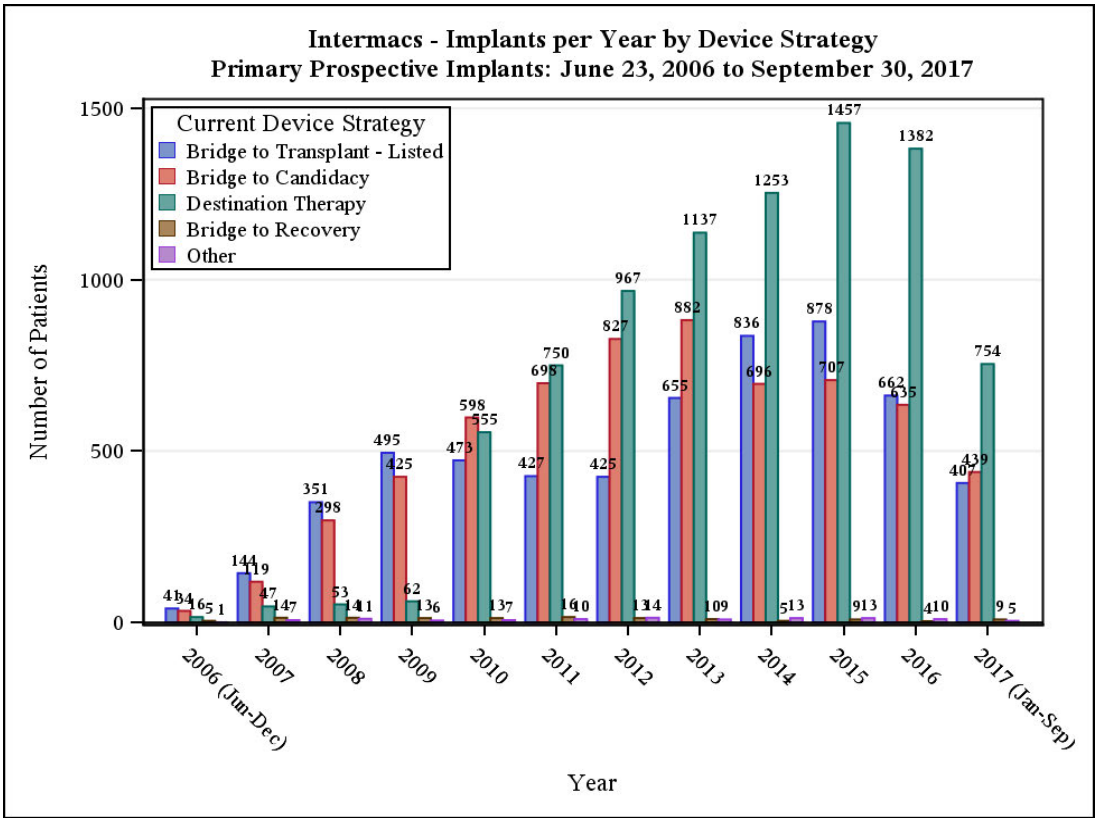
Heart transplantation is the gold standard and the most cost-effective treatment for end-stage heart failure (Hunt and Haddad 2008). While the demand for heart transplantation globally has increased significantly each year, the utilization or recovery of available donor hearts for transplantation has been limited. Based on the Organ Procurement and Transplantation Network (OPTN) 2014 report, 4,323 (approximately 50%) consented, donor hearts in the U.S. are not recovered annually, depriving thousands of patients the gift of new hearts to treat their end-stage heart disease (Israni, et al., 2016) (see Figure 1).

Figure 1: Heart Organ Use in the U.S. in 2014 (Figure DOD7.5 from OPTN/SRTR Annual Data Report 2014) (Israni, et al., 2016)



The donor organ shortage has also led to an increasing utilization of Mechanical Circulatory Support (MCS) devices, which are being used as either a "Bridge to Transplant" or as a replacement for organ transplantation ("Destination Therapy") (Figure 2).

Figure 2: MCS devices implanted in U.S. patients, 2006-September 2017. From INTERMACS Quarterly Statistical Report, 2017. (Kirklin, et al., 2017)



MCS devices are being implanted in patients who are candidates for heart transplant (so-called Bridge to Transplant (BTT) indication) solely as a result of the donor organ shortage. The American Heart Association, ISHLT, The American Transplant Society and investigators in the U.S. and worldwide recognize heart transplant as the "gold standard" treatment and the only curative therapy for end stage heart failure. (Peura, et al., 2012; Katz, et al., 2015; Wilhelm, 2015; Mancini, 2010; Kobashigawa, et al., 2017). In fact, this shortage of donor organs results in approximately 16% of the Status 1A patients listed on the national waiting list for heart transplantation dying or deteriorating so much that they were removed from the waiting list at 12 months (Table 1). Status 1A patients include those who were implanted with MCS devices while awaiting transplant.

Table 1: **United Network for Organ Sharing (UNOS) Statistics on Waiting List Mortality (*Organ: Heart Waiting List Death Rates within 3, 6, and 12 Months after Listing by Medical Urgency Status at Listing for Adult Registrations Added to the Heart Alone Waiting List during 2014-2016)***

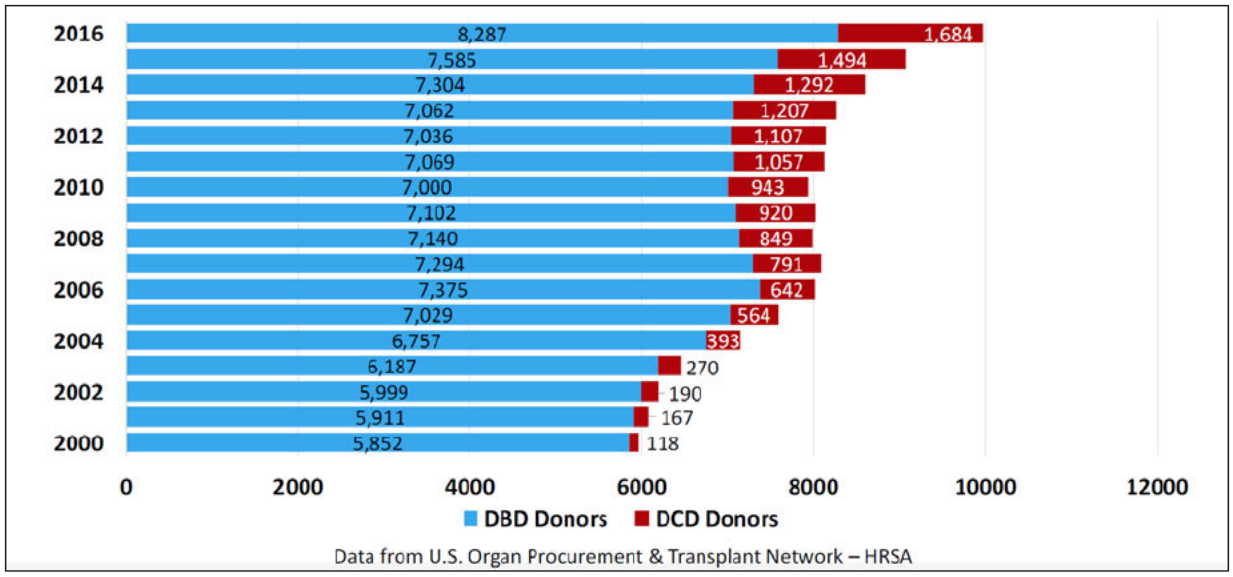
Medical Urgency Status at Listing	Registrations Added	Months After Listing	Number Removed for Death	Death Rate	95% CI of Death Rate
Status 1A	2745	3	335	12.2%	[11.0%, 13.4%]
		6	395	14.4%	[13.1%, 15.7%]
		12	443	16.1%	[14.8%, 17.5%]
Status 1B	5092	3	228	4.48%	[3.94%, 5.07%]
		6	335	6.58%	[5.92%, 7.28%]
		12	452	8.88%	[8.12%, 9.68%]
Status 2	3255	3	146	4.49%	[3.81%, 5.23%]
		6	232	7.13%	[6.28%, 8.04%]
		12	332	10.2%	[9.20%, 11.3%]
All	11092	3	709	6.39%	[5.95%, 6.85%]
		6	962	8.67%	[8.16%, 9.20%]
		12	1227	11.1%	[10.5%, 11.7%]

Note:
1) Death rate was calculated using competing risk method.
2) Death included removal from the waiting list for being too sick.

For the past several decades there has been scientific and clinical interest in the development of ex-vivo heart perfusion (EVHP) with oxygenated and nutrient enriched blood to reduce ischemic injury to the donor heart and potentially enable ex-vivo assessment of metabolic and mechanical function. More recently, EVHP has been used to potentially expand the donor pool to include hearts from donation after circulatory death (DCD).

Until recently, beating hearts from donation after brain death (DBD) donors were the only heart donors used for transplantation worldwide. DBD donors offer the advantage of permitting functional assessment before procurement, allowing for selection of only optimal donor hearts, and more importantly, organs are not subjected to the detrimental effect of warm ischemia in the donor prior to retrieval. The simple preservation method of cold storage became routinely used to transport DBD hearts between the donor and recipient hospitals and adequately preserves these ideal donor hearts. However, during the last 20 years, the number of suitable DBD donors has plateaued while the number of patients diagnosed with end stage organ failure continues to increase. As a result, the waiting list for organ transplantation has grown. To address the organ shortage, DCD donors are being increasingly used to procure donor lungs, livers, and kidneys (see Figure 3 below).

Figure 3: DCD Donors and DBD Donors in the U.S.



However, due to potential damage of warm ischemia in the donor and the functional arrest of the heart that may never recover, DCD donors are **not** utilized for adult heart transplantation in the U.S. In contrast, international transplant centers have been successfully transplanting hearts from DCD donors, using the OCS Heart System for resuscitation, preservation and assessment of these hearts prior to transplantation. The OCS Heart System can minimize the detrimental effects of ischemia because it perfuses the donor heart with warm oxygenated blood. It enables the heart to be resuscitated to full beating state, and importantly enables the transplant team to assess metabolic (lactate production) and perfusion parameters of these hearts to determine their suitability for transplantation. These capabilities are critical when using extended criteria and DCD donor hearts to minimize the risks on the recipients receiving these organs.

Currently, the TransMedics' OCS Heart technology is the only portable system available for ex-vivo maintenance of the donor heart in a metabolically active and beating state.

Specifically, with regard to the challenges posed by DCD donor hearts noted above, the OCS Heart System offers the following advantages and capabilities:

- Resuscitation of the DCD heart into beating physiologic state ex-vivo to enable for the assessment of the donor heart's viability.
- Reduction of the time-dependent ischemic injury 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-dead condition in the body of the donor, which would negatively impact cardiac function if not replenished.
- Assessing the adequacy of the perfusion and metabolic condition of the 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.

In summary, patients listed for heart transplantation due to their end stage heart disease are suffering from a terminal, life-threatening condition. Increasing the number of heart transplants by preserving extended criteria donors and DCD hearts with the OCS Heart System has the potential to provide patients with end stage heart failure with the gold-standard, life-saving treatment.

2. SUMMARY OF PRIOR TESTING AND INVESTIGATIONS

2.1. OCS Heart Preclinical Testing

The OCS Heart System 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.

2.2. Preclinical Animal Testing of OCS Heart System for DCD hearts

Two preclinical animal studies have been published that evaluated the use of the OCS Heart System to preserve DCD hearts in animal models.

2.2.1. Iyer, et al., 2015

This study evaluated the use of the OCS Heart System to preserve DCD hearts in a porcine orthotopic heart transplant model. DCD hearts preserved with the OCS Heart System were compared to DCD hearts preserved using standard cold storage for 4 hours.

All donor hearts were exposed to 30 minutes of warm ischemia in a DCD asphyxia model prior to being flushed with cardioplegia. The comparison of the experimental timeline for the two groups is shown in Figure 4 below. Orthotopic transplantation into recipient animals was then performed.

Figure 4: Comparison of Experimental Timeline for OCS and Control Groups (Figure 1 from Iyer, et al., 2015)

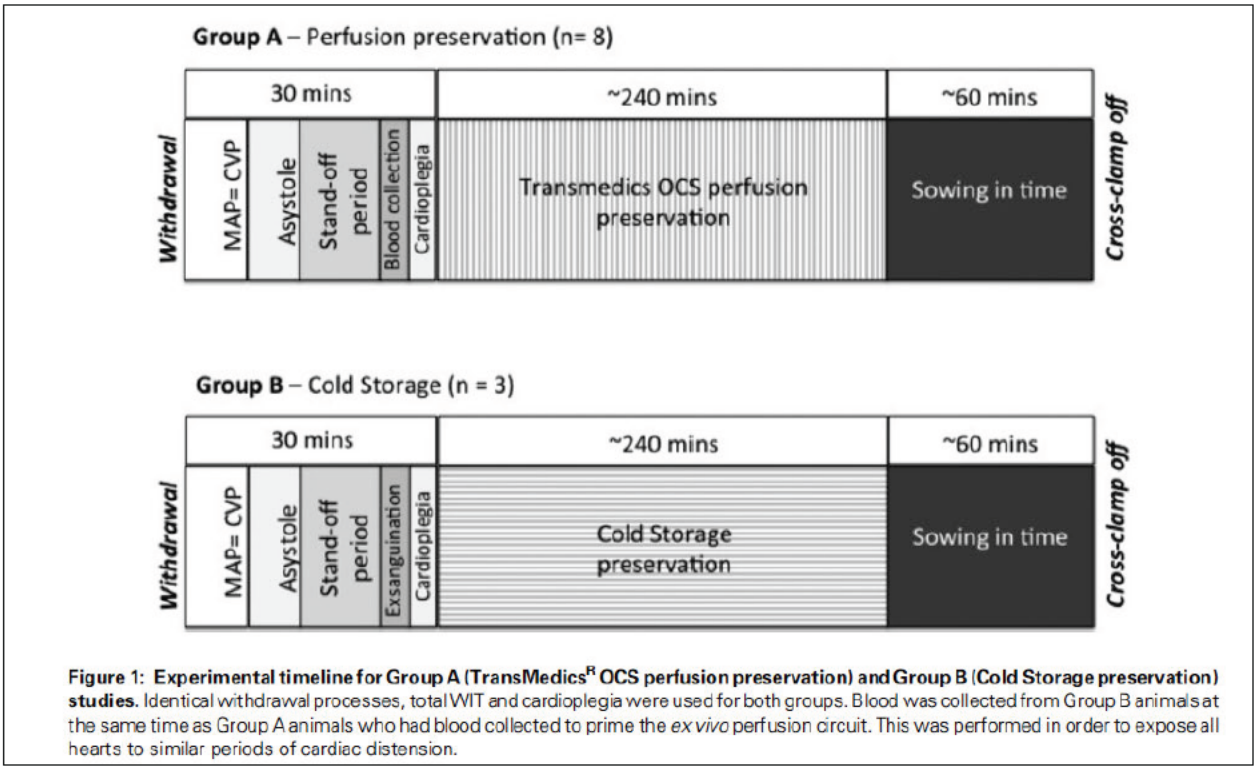


Figure 1: Experimental timeline for Group A (TransMedics® OCS perfusion preservation) and Group B (Cold Storage preservation) studies. Identical withdrawal processes, total WIT and cardioplegia were used for both groups. Blood was collected from Group B animals at the same time as Group A animals who had blood collected to prime the *ex vivo* perfusion circuit. This was performed in order to expose all hearts to similar periods of cardiac distension.

Five of six hearts preserved with the OCS heart system demonstrated favorable lactate profiles and all five could be weaned off cardiopulmonary bypass post-transplant compared to 0 of 3 hearts preserved with cold storage. The authors concluded that DCD hearts preserved with the OCS heart system demonstrated viability before and after transplant, and that human studies of DCD hearts using the OCS Heart System are warranted.

2.2.2. García Sáez, et al., 2015

This study evaluated the use of the OCS Heart System to preserve DCD hearts in an ex vivo porcine model.

Circulatory death was induced in five pigs and the agonal time was calculated as the time between a reduction in blood pressure < 50 mm Hg or a fall in saturation below 70% and the cessation of electrical activity. After an additional 15 minutes of warm ischemia, hearts were procured and instrumented on the OCS and the procured grafts were assessed over a period of 4 hours. The results showed that four hearts were successfully resuscitated on the system with agonal times of 8, 15, 20 and 34 minutes. These grafts had good visual contractility and declining lactate and were considered transplantable. One graft, with agonal time = 34 minutes, had increased lactate and abnormal contractility and was not considered suitable for transplant. One heart with 48 minutes of agonal time could not be resuscitated. The authors compared the hemodynamic parameters during OCS perfusion and degree of edema after explantation with historical control grafts and no significant difference was found (Table 2).

Table 2: Comparison of Hemodynamic Parameters for DCD Hearts Preserved on OCS and Historical Control (standard criteria hearts) preserved on OCS (Table 1 from García Sáez, et al., 2015)

Table – Comparison of hemodynamic parameters during OCS perfusion and degree of edema after explantation from the system between historical control grafts and grafts after cardiocirculatory death.

Hemodynamic parameters	Control OCS	DCD hearts—OCS	P value
Aortic pressure (mm Hg)	62 ± 11	54 ± 7	0.48
Coronary flow (mL/min)	670 ± 40	720 ± 30	0.29
Heart rate (bpm)	89 ± 9	88 ± 13	0.46
Weight gain %	33 ± 6	27 ± 5	0.40
Water content %	84.5 ± 1.6	84.1 ± 0.2	0.372

The authors concluded that the hearts from DCD donors can be successfully resuscitated on the OCS in a scenario that simulates clinical conditions.

2.3. OCS Heart Clinical Testing for DCD Hearts Outside the U.S.

Due to the damage done by warm ischemia and the mechanical arrest in the donor, only DBD donors are currently utilized for adult heart transplantation in the U.S. In contrast, international transplant centers have been transplanting hearts from DCD donors, using the OCS Heart System for resuscitation, preservation and assessment of these hearts prior to transplantation. The OCS Heart System can minimize the detrimental effects of ischemia because it perfuses the donor heart with warm oxygenated blood. It enables the heart to be resuscitated to full beating state, and importantly enables the transplant team to assess metabolic (lactate production) and perfusion parameters of these hearts to determine if their suitability for transplantation. These capabilities are critical when using marginal/questionable and DCD donor hearts to minimize the risks on the recipients receiving these organs.

2.3.1. Messer, et al., 2017

Messer, et al. (2017) has published the results of a study of the OCS Heart System for preserving DCD donor hearts in the UK. This was a single-center observational matched cohort study comparing consecutive patients who received transplants of DCD donor hearts between February 1, 2015, and March 31, 2017, vs. matched recipients who received transplants of DBD donor hearts between February 1, 2013, and March 31, 2017. There was no difference in implant technique or immunosuppressive regimens during this period. DCD hearts were transported and continually perfused on the OCS Heart System. DBD hearts all underwent the current standard of direct procurement and cold storage until transplantation.

DCD heart donors were restricted to Maastricht category III donors, defined as expected death after the withdrawal of life- supportive therapy (WLST). A retrospective cohort of DBD heart transplants,

matched for donor and recipient characteristics, was used as a comparison group. The primary outcome measure of this study was 90-day survival. There were 26 DCD heart transplants performed during the 25-month study period. The use of the OCS Heart System resulted in an 86.7% rate of successful utilization of DCD hearts for transplantation. Survival at 90 days was not significantly different between DCD and matched DBD transplant recipients (DCD, 92%; DBD, 96%; p=1.0). Hospital length of stay, treated rejection episodes, allograft function, and 1-year survival (DCD, 86%; DBD, 88%; p=0.98) were comparable between groups.

Of the 26 DCD hearts transplanted, 12 used Normothermic Regional Perfusion (NRP) before OCS and 14 used Direct Procurement and Preservation (DPP). During the NRP procedure, following circulatory arrest the cerebral circulation was terminated but perfusion was restored to the thoracic and abdominal organs within the donor body. Functional assessments of the heart were performed after which donor blood was collected and the heart was arrested with cold cardioplegia. (NRP will not be used in this study). The DPP procedure followed the standard OCS blood collection and cardioplegic arrest of the donor heart. In the DPP arm, utilization was 77.8% (14/18) and 90-day survival was 86% (12/14).

Figure 5: K-M Survival of Recipients of DCD and DBD Donors (Figure 2 from Messer, et al., 2017)

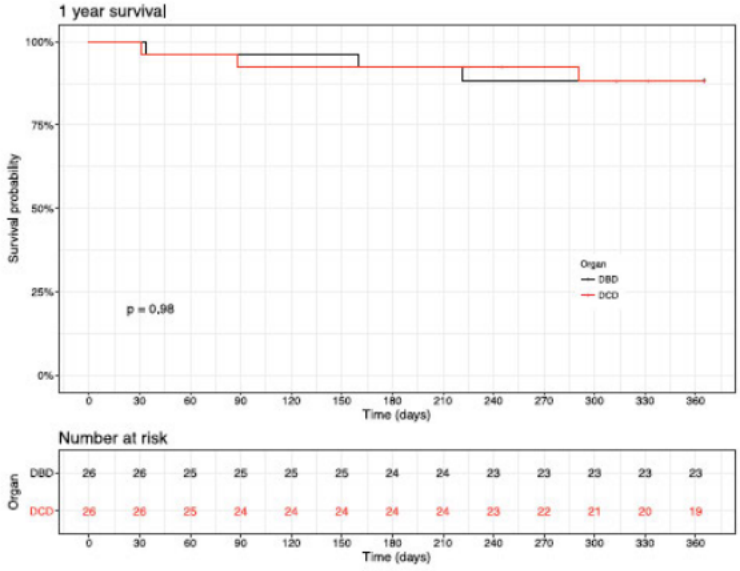


Figure 2 Kaplan-Meier survival of donation after circulatory-determined death (DCD) and donation after brain death (DBD) heart transplantation.

The authors noted that DCD heart transplantation may increase heart transplants by 17% to 30%. During the study period, 84 DBD heart transplants were performed at this institution and the 26 additional DCD heart transplants increased the number of transplants by 33%. The authors concluded that the adoption of DCD heart transplantation can be safely implemented into widespread routine clinical practice.

2.3.2. Dhital, et al. (2015 and 2017)

The first report, published in 2015 in the Lancet, described transplantation of DCD hearts into three recipients (two men, one woman; mean age 52 years). They received Maastricht category III controlled hearts donated after circulatory death from people younger than 40 years and with a

maximum warm ischemic time of 30 min. Donor heart warm ischemic times were 28 min, 25 min, and 22 min, with OCS Heart perfusion times of 257 min, 260 min, and 245 min, respectively. Two patients needed temporary mechanical support. All three recipients had normal cardiac function within a week of transplantation, and, at the time of the report, were alive and recovering well at 176, 91, and 77 days after transplantation.

The second report, published in 2017, described the experience of using the OCS Heart System to preserve DCD hearts at St. Vincent's Hospital in Sydney, Australia. The donors were Maastricht Category III donors, < 40 years of age, no history of cardiac disease or cardiac risk factors, minimal inotropes and an expected warm ischemia time of 30 minutes. All donor hearts were perfused with the OCS Lung System. Time from withdrawal of therapy to cessation of circulation was 4 to 25 minutes (median 14 minutes). Total warm ischemic time was 14 to 28 minutes (median 25 minutes), with the time on OCS from 210 to 410 minutes (mean 302 minutes). Results for 12 patients have been reported. One patient needed mechanical support with IABP and 4 patients required ECMO support. There has been no mortality and all patients have normal biventricular function at 25 to 829 days post-transplant at the time of the report. The authors concluded that excellent graft and recipient survival can be achieved from transplantation with DCD hearts using the OCS Heart System.

2.3.3. García Sáez, et al. (2016, 2017)

García Sáez, et al. (2016) reported on the outcomes of 2 recipients with long-term left ventricular assist device (LVAD) support who were successfully transplanted with DCD hearts preserved on the OCS Heart System despite the adverse donor/recipient risk profile. The authors noted "The ability to assess graft viability is of particular importance in DCD HTx, where, in contrast to the DBD setting, the donor organ has invariably been subjected to a sustained ischemic insult before procurement. We deliberately prolonged OCS support duration to allow comprehensive graft assessment and to achieve surgical preparedness in technically demanding recipients with LVADs in situ." In this report, the two patients were alive and well 290 and 291 days after transplantation.

This same author followed up with a report of 5 high-risk recipients (García Sáez, et al., 2017). This included three recipients with LVADs and one subject who was undergoing a second heart transplantation. All patients received DCD heart transplants preserved on OCS. Following transplant, two patients developed primary graft dysfunction requiring mechanical support. One patient died within the first 30 days post-transplant (the patient who had undergone a second heart transplant). The remaining 4 patients are well and alive at a mean 324 days post-transplant (range 18-496 days).

2.4. Additional Clinical Studies of the OCS Heart System for Standard Criteria and Extended Criteria Donor Hearts

TransMedics has conducted two previous IDE studies of the OCS Heart System in Standard Criteria and Extended Criteria Donor Hearts. These studies provide supporting evidence for the safety of the OCS Heart System for this investigation and are briefly described below.

- The OCS Heart EXPAND trial was a prospective, single arm study of 75 heart transplant recipients who received hearts preserved on the OCS. These hearts were from extended criteria donors, i.e., those that are seldom transplanted in transplant institutions today without the OCS. The results demonstrated:

  - Utilization rate of 80.6% of donor hearts that are rarely used for transplantation today. These donor hearts were refused by other (non-EXPAND) centers an average of 65.6 times but were able to be preserved and 80.6% were transplanted successfully in this study.
  - The incidence of ISHLT severe PGD was 10.7%, and the incidence of ISHLT moderate or severe PGD was 14.7%. These rates compare favorably with contemporary literature reporting PGD rates post-heart transplantation using the ISHLT criteria.
  - Survival at 30 days, 6 months, and 12 months was 95%, 88%, and 84%, respectively.
- The FDA also approved a Continued Access Protocol (CAP) for EXPAND called the EXPAND CAP. The study is on-going and data are still being collected, but based on the available data the results show:
  - 38 donor hearts were preserved and assessed on the OCS Heart System.
  - The utilization rate is 89.5%, with 34 of 38 extended criteria donor hearts successfully transplanted.
  - The first 20 transplanted patients have reached a minimum of 30-day follow-up and all survived (100% survival at 30-days).
  - No severe LV or RV ISHLT PGD has been reported among the first 20 subjects transplanted.
- PROCEED II was the first pivotal study of the OCS Heart System. It was a randomized study of the OCS Heart System compared to standard of care cold storage, and it enrolled standard criteria donor hearts. The study met its primary endpoint and non-inferiority was shown in 30-day survival, as well as in the secondary endpoint, i.e., cardiac graft-related SAEs. Longer-term data, obtained from the SRTR database, showed lower survival rates for the OCS group at 2-3 years of follow-up; however, the incidence of cardiac graft-related deaths was similar and other deaths were typical for heart transplant recipients (late infection, malignancy, multi-organ failure). The results of this study were published in the Lancet (Ardehali, et al., 2015).
- Studies of the OCS Heart System for preservation of standard criteria donor hearts conducted outside the U.S. at hospitals in Germany and the UK showed improved rates of survival and lower rates of PGD for OCS compared to standard of care cold storage (Koerner, et al., 2014).

2.5. Overall Summary of Clinical Data to Support Initiation of OCS Heart DCD Trial

In summary, studies of the OCS Heart System for the preservation of DCD hearts have been performed outside of the U.S. These studies have shown 77.8 - 86.7% utilization rate, with 90-day and 1-year survival comparable to outcomes obtained with standard criteria donor hearts preserved using cold storage standard of care.

In addition, the OCS Heart EXPAND trial, the OCS Heart EXPAND CAP and studies of the use of OCS to preserve extended criteria hearts performed outside the U.S. shows high utilization rate, with good

clinical outcomes, demonstrating the ability of the OCS Heart System to expand the potential pool of donor organs. These data provide strong support for the initiation of the DCD Heart Trial.

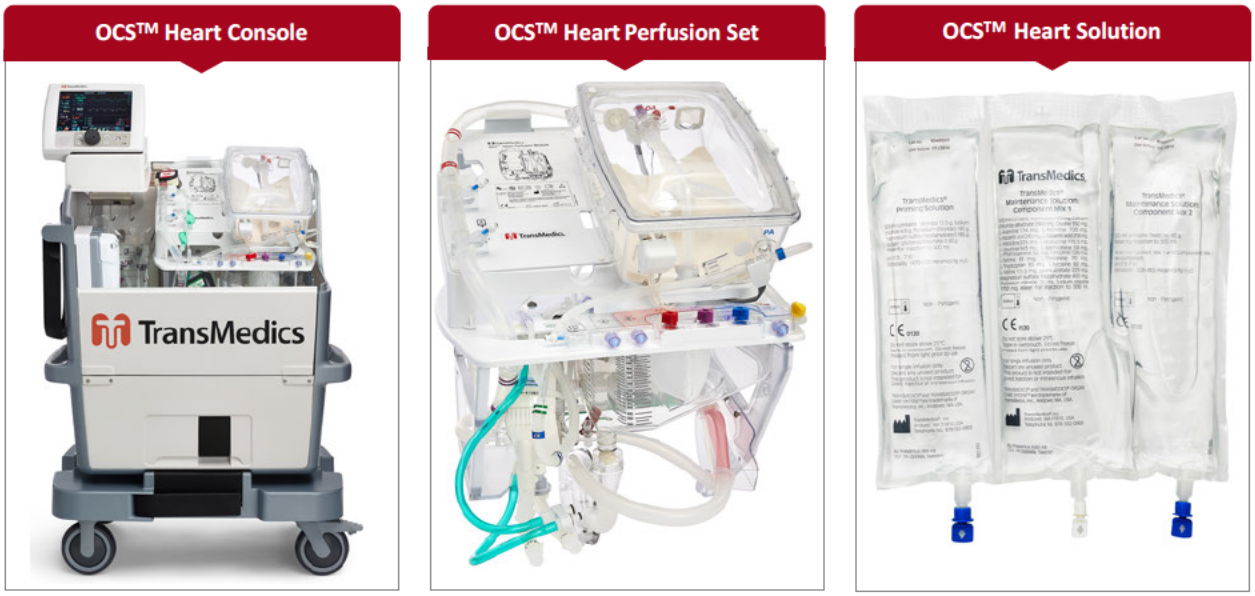
3. DEVICE DESCRIPTION

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:

- OCS Heart Console
- OCS Heart Perfusion Set – comprised of Heart Perfusion Module (HPM) and Accessories
- OCS Heart Solution Set

These major components are shown in Figure 6 below.

Figure 6: Figures of the OCS Heart System



3.1. Description of Major Components

3.1.1. OCS Heart Console

The OCS Heart Console is the reusable, non-sterile portable enclosure incorporating the electronics, software, fluid pumping systems, monitoring systems, power supply, batteries, gas cylinder, mobile base and Wireless Monitor. The Wireless Monitor displays information and allows the user to adjust certain settings.

The OCS Heart Console provides a rigid compartment to house and securely connect to the HPM during transport. The OCS Heart Console connects to a mobile base with locking wheels.

3.1.2. Heart Perfusion Set (HPS)

The Heart Perfusion Set (HPS) consists of the Heart Perfusion Module (HPM) and Disposable Accessories. The HPM provides a closed circulatory system to protect, maintain and support the

heart. It uses a physical conduit to connect to the heart, incorporates various sensors, and interfaces with the OCS Heart Console to oxygenate, warm and circulate the perfusate.

The accessories are intended to:

- Collect and process the donor blood
- Prime and then infuse the OCS Heart Solution to the HPM
- Connect the heart to the HPM circuit
- Facilitate monitoring of the heart operation
- Infuse cardioplegia to terminate the preservation.

The HPM provides the sterile blood circuit and protected environment for a heart within the OCS. It is designed as a single-use, pre-assembled module that mounts into the OCS. The heart is instrumented within the heart chamber of the HPM. The Wireless Monitor displays measurements made within the HPM. The HPM includes:

- Dual lid heart-specific heart chamber
- Integrated and easily accessible blood sampling and de-airing manifold
- Integrated pulsatile pump head interface
- Integrated low shear titanium blood warmer
- Integrated blood oxygenator (or gas exchanger)
- Integrated sensors (pressure and temperature) and circuitry to communicate with the Console.

3.1.3. OCS Heart Solution Set

The OCS Heart Solution Set consists of two proprietary heart preservation solutions, a Priming Solution and a Maintenance Solution, to replenish the nutrients and hormones (adenosine) that the metabolically active donor heart requires. The solutions are packaged in a three-chamber bag (nominal volume of 500 ml per chamber). At the time of use, the Priming Solution (500 ml) is dispensed into the HPM. The Maintenance Solution is manufactured as two component solutions (500 ml each) that are individually manufactured and then mixed immediately before infusion into the HPM. Additives are required at the time of use. The additives are not supplied by TransMedics, and are added by user.

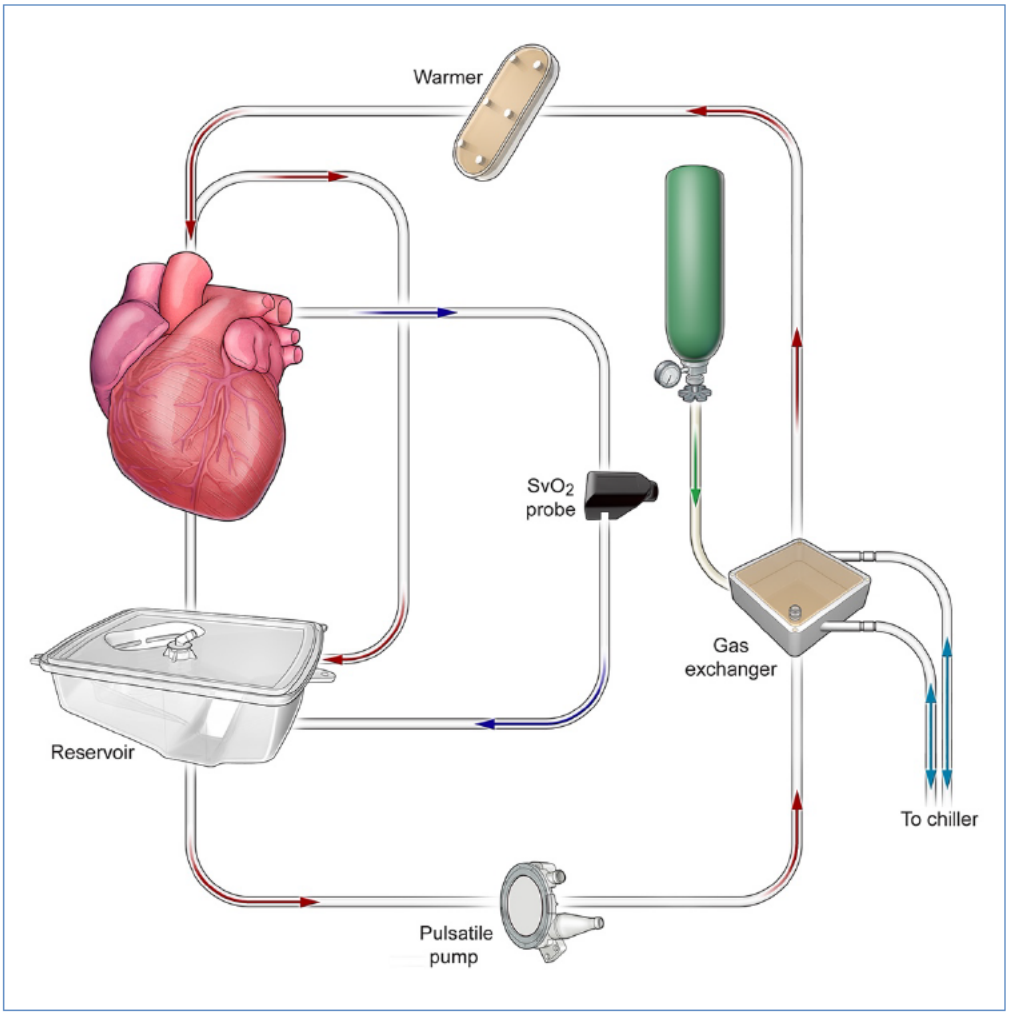
The OCS Heart Solution Set is not intended to be administered directly to the donor or the recipient. The donor heart is arrested prior to removal using a standard cardioplegia solution. Prior to transplantation into the recipient, the donor heart is arrested on the OCS through the use of a standard cardioplegia solution, at which time the perfusate (including the donor blood, Priming Solution and Maintenance Solution) are flushed from the donor heart.

3.1.4. Mode of Action - Overview

The OCS Heart System preserves the heart in a near-physiological, beating state by perfusing the heart with a warmed, donor-blood based perfusate that is supplemented with nutrients and oxygen in a controlled and protected environment referred to as the circuit. The circuit is illustrated in

Figure 7 below. The OCS contains a pulsatile pump that directs flow through the gas exchanger, to be oxygenated, and then through the blood warmer and then to the aorta of the donor heart. An additional perfusate component, known as the TransMedics Maintenance Solution, is infused into this circuit. The heart consumes oxygen and nutrients as the blood travels from the aorta through the coronary arteries and returns blood to the circuit through its pulmonary artery. The OCS maintains the blood at a constant temperature, oxygenates the perfusate at a constant rate, and provides perfusate in a pulsatile flow at a constant rate.

Figure 7: Schematic of the OCS Heart System Fluid Flow



4. TRIAL OBJECTIVES

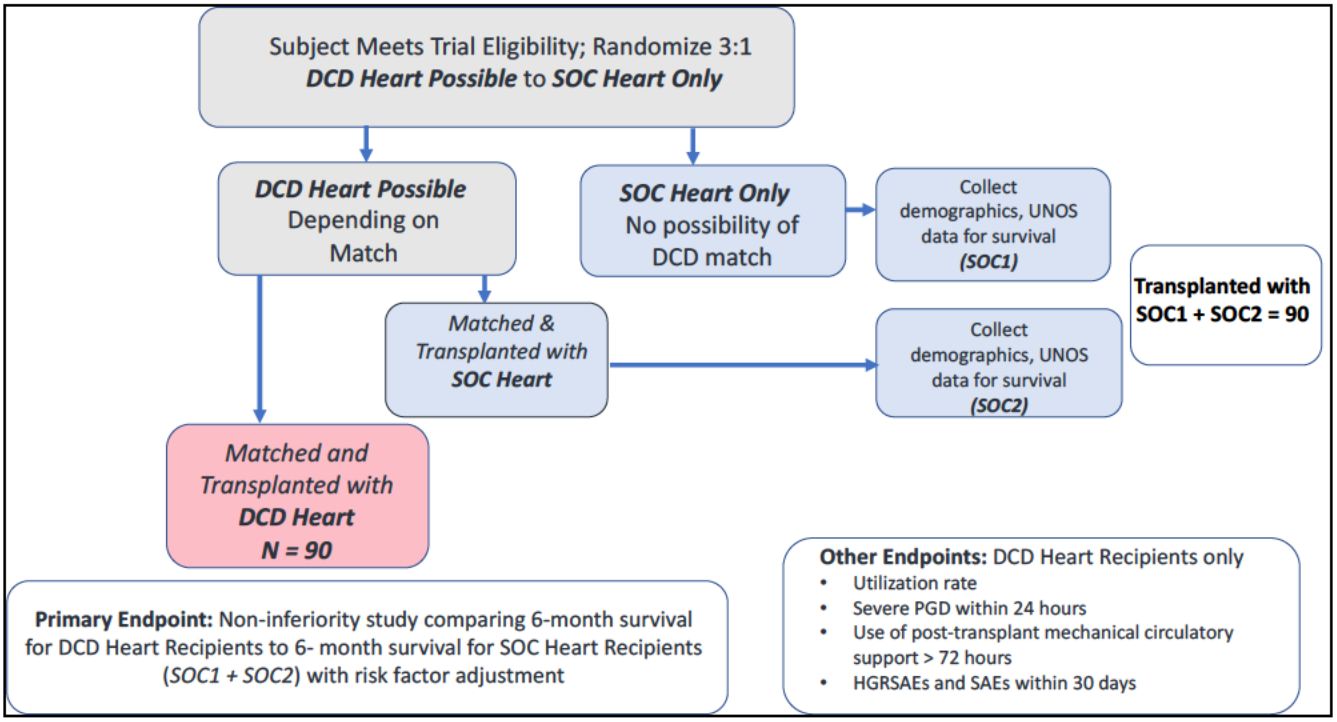
The objective of the DCD Heart Trial is to evaluate the effectiveness of the OCS Heart System to resuscitate, preserve and assess hearts donated after circulatory death for transplantation to increase the pool of donor hearts available for transplantation.

4.1. Trial Design

A prospective, randomized and concurrent controlled, non-inferiority pivotal trial in which subjects who receive a DCD donor heart transplant will be compared to subjects who receive a standard

criteria donor heart transplant (SOC1 and SOC2 - from both randomized and concurrent control groups), adjusting for differences in risk factors. The trial design is illustrated in Figure 8 below.

Figure 8: OCS Heart DCD Heart Trial Design



4.2. Trial Size and Subject Follow-up

A maximum of 25 participating sites with 90 transplanted DCD heart recipients and 90 SOC heart transplant recipients. Follow-up data for the SOC recipients will be obtained from UNOS/OPTN standard database for transplant recipients through 5 years after transplantation.

Subjects who receive a DCD heart transplant will be followed for 12 months from the date of transplantation (some of which will be post-market). Data from UNOS/OPTN transplantation database will be obtained through 5 years after transplant. The follow-up assessments are summarized in Appendix 2.

5. TRIAL ENDPOINTS

5.1. Primary Endpoint

A non-inferiority comparison of patient survival at 6 months post-transplant between recipients of DCD donor hearts preserved on the OCS Heart System (***DCD Heart Transplanted Recipient Population)*** and recipients of standard criteria donor hearts preserved using cold storage (***SOC1 + SOC2, SOC Heart Transplanted Recipient Population***), adjusting for risk factors.

5.2. Secondary Endpoint

Utilization Rate is defined as the number of eligible DCD donor hearts that met the warm ischemic time limit and were instrumented on the OCS Heart System that meet the acceptance criteria for

transplantation after OCS Heart preservation divided by the total number of eligible DCD donor hearts that met the warm ischemic time limit above and were instrumented on the OCS Heart System.

5.3. Safety

The safety endpoint is defined as the incidence of Heart Graft-related Serious Adverse Events (HGRSAEs) in the first 30 days post-heart transplantation in the DCD Heart Transplanted Recipient Population, defined as the following adverse events (at most one per type):

- Moderate or Severe heart PGD (left or right ventricle) (not including rejection or cardiac tamponade) according to ISHLT consensus manuscript (as defined in Appendix 1 of this protocol).
- Primary graft failure requiring retransplantation.

This endpoint is calculated for the DCD Heart Transplanted Recipient Population only.

5.4. Other Endpoints

Other endpoints collected for the DCD Heart Transplanted Recipient Population include:

- Patient and graft survival at 30 days post-transplant
- Patient and graft survival at 30 days and initial hospital discharge, if later than 30 days
- Severe PGD (left or right ventricle) (not including rejection or cardiac tamponade) according to ISHLT consensus manuscript (as defined in Appendix 1 of this protocol)
- Use of post-transplant mechanical circulatory support (LVAD, RVAD, BiVAD) for > 72 hours immediately post-transplant.

Other endpoints calculated for both the DCD Heart Transplanted Recipients and the SOC Heart Transplanted Recipients (SOC1+SOC2) include:

- Patient survival at 1 year after transplant (collected post-approval); comparison of ***DCD Heart Transplanted Recipients*** and ***SOC Heart Transplant Recipients*** (***SOC1 + SOC2***) through UNOS/OPTN database.

6. TRIAL POPULATION

The trial will include heart transplant recipients, aged 18 to 49 years, inclusive, at up to 25 investigational sites in the U.S. Medicare beneficiaries with a clinical need for transplantation will be treated in the same manner as patients not covered by a Medicare plan. The rules of participation and results of the study apply to Medicare and non-Medicare covered patients in the same manner.

6.1. DCD Donor Eligibility Criteria

Donor Inclusion Criteria

- Maastricht Category III DCD donor, defined as expected death after the withdrawal of life-supportive therapy (WLST)

- Donor age 18-49 years old inclusive
- Warm ischemic time (WIT) ≤ 30 mins, with warm ischemic time defined as: Time from when mean systolic blood pressure (SBP) is < 50 mmHg or peripheral saturation < 70% to aortic cross-clamp and administration of cold cardioplegia in the donor.

Donor Exclusion Criteria

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

- Previous cardiac surgery;
- Known coronary artery disease;
- Cardiogenic shock or myocardial infarction;
- Sustained terminal EF of ≤ 50%; or
- Significant valve disease except for competent bicuspid aortic valve.

6.2. Standard of Care Donor Eligibility Criteria

Standard criteria donor hearts will be screened and determined to be eligible for transplant according to the standard of care at each institution. Standard of care donor hearts that are eligible for transplantation will be preserved according to the standard practices at each institution.

6.3. Recipient Eligibility Criteria

Recipient Inclusion Criteria

- Primary heart transplant candidates
- Age ≥ 18 years old
- Signed: (1) written informed consent document; (2) authorization to use and disclose protected health information; and (3) consent to TransMedics' use of recipients' UNOS/OPTN data and consent to TransMedics' use of recipients' INTERMACS data.

Recipient Exclusion Criteria

- Prior solid organ or bone marrow transplant
- Chronic use of hemodialysis or diagnosis of chronic renal insufficiency
- Multi-organ transplant
- Investigator unwilling to randomize to either arm.

6.4. Screening and Treatment

Primary heart transplant candidates will be screened for trial eligibility. Every eligible candidate will be asked to participate. Subjects will be randomized into two groups: ***DCD Heart Possible*** and ***SOC Heart Only*****.** Subjects who are randomized into the ***SOC Heart Only*** group will have no possibility for a DCD Heart transplant. Subjects randomized into the ***DCD Heart Possible*** group have the possibility of receiving either a DCD heart or an SOC donor heart, depending upon the donor match. In order to obtain enough subjects with DCD donor heart transplants, subjects will be randomized 3:1 to the ***DCD***

Heart Possible and ***SOC Heart Only*** arms, respectively. Follow-up survival data for transplanted subjects in ***the SOC Heart Transplanted Recipient (SOC1)*** group will be obtained from the UNOS/OPTN standard database for transplant recipients. Upon receiving a donor heart match and after confirmation of eligibility, SOC Heart transplanted recipients will have demographic information collected and will then exit the study and undergo standard heart transplantation according to the institution's standard of care.

In the ***DCD Heart Possible*** arm, if a screened and eligible subject is matched with an SOC donor heart before an eligible DCD donor heart becomes available and is transplanted, these subjects will form a second ***SOC Heart Transplanted Recipient group (SOC2*****)**. Follow-up survival data for subjects in the ***SOC2*** group will be obtained from the UNOS/OPTN standard database for transplant recipients. Upon receiving a donor heart match and after confirmation of eligibility, SOC Heart transplanted recipients will have demographic information collected and will then exit the study and undergo standard heart transplantation according to the institution's standard of care.

Data will be collected according to this protocol for subjects in the DCD Heart Possible arm who receive a DCD Heart match and are transplanted with the DCD heart as outlined in this protocol (***DCD Heart Transplanted Recipient group).***

6.5. DCD Heart Subject Enrollment and Screen Failures

As part of the screening process for subjects in the DCD Heart Transplanted Recipient population, the following must occur:

- Recipient must be matched with a donor heart that meets eligibility criteria for DCD Heart Trial;
- Recipient must meet eligibility criteria for this DCD Heart Trial;
- The matched DCD donor heart must be accepted for transplantation in the donor chest by the transplant surgeon or designee (including meeting the Warm Ischemic Time limit outlined in this protocol);
- The matched donor heart must be instrumented on the OCS;
- The donor heart matched to this recipient must meet transplantability criteria per Section 7.5.1 of the protocol following OCS Heart System instrumentation; and
- The recipient must be transplanted with the DCD heart instrumented on OCS.

A subject will be considered a screen failure under any of the following conditions:

- The matched DCD donor heart is not accepted for transplantation in the donor chest by the transplant surgeon or designee (including meeting the Warm Ischemic Time limit outlined in this protocol).
- The matched DCD donor heart is not instrumented on the OCS.
- The donor heart matched to this recipient fails to meet transplantability criteria per Section 7.5.1 of the protocol following OCS Heart System instrumentation (i.e., donor heart turndown).

- The recipient fails to meet inclusion/exclusion criteria on the day of the potential transplant after an eligible DCD donor heart is instrumented on the OCS Heart System and accepted for transplantation following OCS preservation.
- Logistical reasons prevent transplantation of DCD donor heart instrumented on the OCS Heart System that meets acceptance criteria for transplant following OCS preservation (e.g., transplant center or OPO issues, transportation or allocation issues, surgeons or ORs are unavailable).

A subject will be considered enrolled in the DCD Heart arm when the subject is transplanted with the OCS-instrumented organ. Trial data will be collected only for those subjects considered enrolled in the trial.

Subjects who are screen failures that remain eligible for the study will return to the waiting list for another heart transplant. Since these are subjects in the DCD Heart Possible arm, depending on the donor match, this next transplant may be either a DCD Heart or an SOC heart.

7. PRE-OPERATIVE TRIAL PROCEDURES

7.1. Subject Identification

Those patients who initially appear eligible for the trial will have the trial explained to them, be invited to participate, and will be asked to sign an informed consent. Subjects will then be randomized to either SOC Heart Only or DCD Heart Possible arms as described above. When a matching eligible donor heart becomes available, the inclusion and exclusion criteria for the recipient will be re-verified. If the recipient is no longer eligible for the trial, they will be considered a screen failure and they will exit the study, and no information will be collected for these subjects.

7.2. Recipient Day of Transplant Assessment

The purpose is to conduct a final assessment of whether the potential recipient still meets the eligibility criteria. Specific data to be collected can be found in the Schedule of Assessments in Appendix 2.

7.3. Donor Screening and Acceptance for SOC Hearts

The investigator or a member of her/his transplant team will evaluate the donor and the quality and suitability of the heart for transplantation, according to his or her standard practice. If the donor heart does not meet criteria for transplantation it will be considered a “dry run” and no information on this donor heart will be collected.

7.4. Donor Screening and Acceptance for DCD Hearts

The investigator or a member of her/his transplant team will evaluate the donor and the quality and suitability of the DCD heart for: (1) transplantation, according to his or her clinical judgement and (2) eligibility for the DCD Heart arm of this study, including meeting the warm ischemic time limit outlined in this protocol. If the donor heart does not meet the above criteria, it will be considered a “dry run” and no information on this donor heart will be collected.

If the donor heart meets the above criteria and is preserved on OCS, baseline characteristics, demographics and other donor information will be collected at this visit. Parameters to be collected can be found in the Schedule of Assessments in Appendix 2.

7.5. DCD Donor Heart Retrieval and OCS Preservation and Assessment

Upon acceptance into the trial, the investigators will retrieve and preserve the donor heart according to the OCS Heart Instructions for Use (IFU).

7.5.1. Donor Heart Acceptance/Rejection for Transplantation after OCS Preservation

Donor hearts preserved on the OCS should have stable parameters throughout perfusion after initial stabilization period (defined as the time period during which perfusion is initiated and primary parameter adjustments are made).

Accept for Transplantation

Donor hearts preserved on the OCS Heart System to be maintained within the following target ranges:

- Stable or downward trending lactate after initial adjustments of the OCS Heart perfusion parameters to achieve adequate perfusion to the donor heart
- Stability of OCS Heart Perfusion Parameters within range:
  - AOP 40-100 mmHg.
- Transplanting surgeon and/or heart failure cardiologist must clinically accept the OCS perfused donor heart for transplantation.

Reject for Transplantation

- Transplanting surgeon and/or heart failure cardiologist clinically unsatisfied with donor heart condition/performance on the OCS Heart System at final evaluation.
- Unstable and rising arterial lactate despite maneuvers to optimize perfusion parameters.

Note: certain donor hearts may require perfusion with parameters outside of these guidance ranges. Acceptance for transplantation should be primarily based on an acceptable lactate trend.

Any decision to turndown hearts after preservation and assessment on OCS Heart System should be documented on the appropriate CRF. Samples should be sent to the central core lab for assessment of any inherent cardiac pathology that was not diagnosed at retrieval of the donor heart.

8. TRANSPLANT, IMMEDIATE POST-OPERATIVE AND LONG-TERM FOLLOW-UP FOR DCD HEART TRANSPLANTED RECIPIENTS ONLY

8.1. Transplant Details

The following information concerning the transplant procedure will be collected:

- The organ recipient unique post-transplant patient identifier
- Warm ischemic time as defined in this protocol

- Total cross clamp duration in minutes (from donor cross-clamp application to removal of cross-clamp in the recipient)
- Pre-OCS cold ischemia time (time from donor cross clamp until start of perfusion on OCS)
- 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.

8.2. Post-transplant Functional Assessments Day 0 – Day 30

- Heart PGD Surveillance in the first 24 hours
- Initial use of Mechanical Circulatory Support in the first 72 hours
- Inotropic Support for first 24 hours from T0 to T24 hours after ICU admission
- Echocardiogram results within the first 24 hours post-transplant (if available) starting from ICU admission
- Right Heart Catheter Data (not required; data collected only if performed as part of institution's standard of care)
- Initial Post-Transplant ICU Stay
- Initial Post-Transplant Hospital Stay
- Patient and Graft Survival at Day 30 will be assessed.
- Serious Adverse Events*:* All SAEs will be collected for the first 30 days post-transplant. SAEs will be followed until the investigator designates the event to be either resolved or its effect on the patient's condition stabilized.

8.3. Long-term Follow-up: 6 and 12 months

Follow-up data collection will be conducted at 6 months (± 30 days) and 12 months (± 60 days) post-transplant to evaluate patient survival, graft survival and diagnosis of cardiac allograft vasculopathy. These follow-ups may be performed by phone.

8.4. Evaluation of Adverse Events for DCD Heart Recipients Only

Only serious adverse events (SAEs) and Heart Graft-Related SAE's (HGRSAEs) will be captured in this study (DCD Heart Transplanted Recipients only).

8.4.1. Serious Adverse Events (SAEs)

Serious adverse events will be collected only through Day 30 post-transplant. 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.

8.4.2. Heart Graft-Related SAEs (HGRSAEs)

Heart Graft-related SAEs (HGRSAEs) are defined as:

- Moderate or Severe heart PGD (left or right ventricle) (not including rejection or cardiac tamponade) according to ISHLT consensus manuscript as defined in Appendix 1 of this protocol.
- Primary graft failure requiring re-transplantation.

HGRSAEs will be collected from the time a subject is transplanted with the OCS DCD Heart until the completion of the 30-day follow-up evaluation. A HGRSAE will be followed until resolution or stabilization of the event.

8.4.3. Unanticipated Adverse Device Effect (UADE)

The investigator will assess each serious adverse event for whether it is anticipated or unanticipated using the list specified in Section 8.4.4 below.

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.

8.4.4. Anticipated SAEs

Anticipated SAEs that are associated with heart transplant procedures within the first 30 days after heart transplant includes, but is not limited to:

- Acute rejection
- Atrial and ventricular arrhythmias
- Bleeding (major)
- Hemodynamic instability
- Death
- Fever
- Infection
- 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
- GI bleeding
- 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
- Anastomotic 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

8.4.5. Reporting of Adverse Events

Unanticipated adverse device effects (UADE) should be reported to TransMedics, Inc., within 48 hours of the time the investigator learns of the event, but in no case later than 5 working days after learning of the event.

All SAE information will only be collected from transplant through day 30. SAEs should be entered into the study database as soon as possible. SAE will be followed until the investigator designates the event to be either resolved or its effect on the patient's condition stabilized. Details related to treatment of the SAE will also be collected.

8.4.6. Relationship of an SAE or HGRSAE to OCS Heart System

The investigator will assess the relationship of the HGRSAE to the OCS Heart System. 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.
- **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 OCS Heart and the event.
- **Unrelated:** There is no relationship between preservation with the OCS Heart and the adverse event.

8.4.7. Severity

The investigator will rate the severity of the serious 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.

8.4.8. Pre-Existing Conditions

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

9. OCS HEART TRAINING RUNS

Prior to transplanting any DCD hearts in this study, all investigators will complete one or two training runs. The purpose of these training runs is to allow the investigator and the surgical team to become familiar with the procurement of DCD hearts, specifically, the warm ischemia inclusion criteria, and to obtain experience in instrumenting and resuscitating DCD hearts on the OCS Heart System. The donor organs procured and instrumented in the training runs are not intended for transplantation. The results of the training runs will not be included in any data analyses, including the calculation of the utilization rate.

10. STATISTICAL METHODS

10.1. 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.

10.2. Analysis Populations

10.2.1. DCD Heart Transplanted Recipient Population

The ***DCD Heart Transplanted Recipient Population*** will consist of all eligible recipients who are transplanted with an eligible DCD donor heart that met the warm ischemic time limit defined above, preserved on OCS and met the transplantability criteria. The analyses of all effectiveness and safety endpoints, except the utilization rate, will be based on the DCD Heart Transplanted Recipient Population.

10.2.2. OCS Heart Population

The OCS Heart Population will consist of all eligible donor hearts that met the warm ischemic time limit above and were instrumented on the OCS Heart System. The analysis of utilization rate will be based on the OCS Heart population.

10.2.3. SOC Heart Transplanted Recipient Population

The ***SOC Heart Transplanted Recipient Population*** will consist of all recipients who received a standard criteria donor heart (***SOC1 + SOC2*** as defined in Section 6.4).

The analyses of the primary endpoint and of patient survival at one year after transplant will be based on the DCD Heart Transplanted Recipient Population and the SOC Heart Transplanted Recipient Population.

The analyses of: (1) patient and graft survival at 30 days post-transplant; (2) patient and graft survival at 30 days and at initial hospital discharge if longer than 30 days; (3) the use of post-transplant mechanical circulatory support (LVAD, RVAD, and BiVAD) for > 72 hours immediately post-transplant; (4) Severe heart PGD (left or right ventricle) (not including rejection or cardiac tamponade) according to ISHLT consensus manuscript (as defined in Appendix 1 of this protocol); and (5) HGRSAEs and SAEs will be based on the DCD Heart Transplanted Recipient Population.

10.3. Statistical Analysis

10.3.1. Primary Endpoint

The primary endpoint is a comparison of survival at 6 months for DCD heart transplanted recipients and standard criteria heart transplanted recipients (SOC1 + SOC2 as defined in Section 6.4), adjusting for differences in risk factors. This is a non-inferiority study.

Risk Factors

We will adjust for the known donor and recipient risk factors for mortality shown in the list below[2]:

[2] Cardiac Donor Risk Factors Predictive of Short-Term Heart Transplant Recipient Mortality: An Analysis of the United Network for Organ Sharing Database. Trans Proc. 2015 Dec; 47(10): 2944-2951., Heart Transplant Survival based on Recipient and Donor Risk Scoring: A UNOS Database Analysis, ASAIO J., 2016; 62:297-301. Report from the American Society of Transplantation Conference on Donor Heart Selection in Adult Cardiac Transplantation in the United States. Am.J.Transplant, 2017; 17:2559-2566

Donor Variables:

- Donor Age ≥ 55 years
- Gender mismatch (female donor to male recipient).

Recipient Variables:

- Age ≥ 65
- LVAD, ECMO or IABP prior to transplant

For continuous baseline characteristics, two-sided, two-sample t-tests will be used to test for a difference in means between treatment groups. For categorical baseline characteristics, the chi-square test will be used to test for a difference in proportions between treatment groups. We will adjust the analysis of the primary endpoint for any of these baseline characteristics for which there is a statistically significant difference (p-value < 0.15) between the treatment groups.

The null and alternative hypotheses for the primary endpoint are as follows:

H_0: $p_{SOC} - p_{DCD} \geq 0.20$

vs.

H_1: $p_{SOC} - p_{DCD} < 0.20$

where p_{DCD} and p_{SOC} represent the true survival proportions at 6 months for DCD and SOC heart transplant patients, respectively.

The analysis of this endpoint will be performed using a linear probability model, with the following terms in the model: (1) treatment; (2) all of the known donor and recipient risk factors listed previously; and (3) any of the potential risk factors listed above for which there is a statistically significant difference between treatment groups. The p-value for the test of the null hypothesis will be obtained based on a statistic for the difference (SOC - DCD) in least squares means (actually proportions rather than means) for each treatment minus the non-inferiority margin of 0.20 all divided by the standard error of the difference in the least squares means and assuming an approximate normal distribution. The test will be conducted at the 0.05 level of significance.

10.3.2. Secondary and Other Endpoints

Secondary Endpoint:

Utilization Rate, defined in Section 5.2

Other Endpoints:

DCD Heart Transplanted Recipients only:

- Patient and graft survival at 30 days post-transplant
- Patient and graft survival at 30 days post-transplant and at initial hospital discharge, if later than 30 days
- Severe heart PGD (left or right ventricle) (not including rejection or cardiac tamponade) according to ISHLT consensus manuscript (as defined in Appendix 1)

- Use of post-transplant mechanical circulatory support (LVAD, RVAD, BiVAD) for > 72 hours immediately post-transplant.

DCD Heart Transplanted Recipients and SOC Heart Transplanted Recipients:

- Patient survival at one year after transplant (collected post-approval and collected from UNOS for SOC Heart Transplanted Recipients).

Each endpoint will be summarized using counts and percentages and an exact (Clopper-Pearson) 95% confidence interval for the true percentage based on the binomial distribution. Patient survival at one year after transplant will be summarized for both the DCD Heart Transplanted Recipient and SOC Heart Transplanted (SOC1 + SOC2 as defined in Section 6.4) Recipient populations.

Comparisons of recipient demographics and baseline characteristics and of patient survival at 6 months will be performed for the following treatment groups (as defined in Section 6.4):

- SOC1 vs SOC2
- DCD Heart vs SOC1
- DCD Heart vs SOC2.

Continuous demographic and baseline characteristics will be summarized by treatment group using descriptive statistics (mean, standard deviation, median, minimum, and maximum). Categorical demographic and baseline characteristics and patient survival at 6 months will be summarized by treatment group using counts and percentages. For continuous variables, comparisons of treatment groups will be performed using two-sided, two-sample t-tests. For categorical variables, comparisons will be performed using Fisher's Exact Test.

10.4. Safety (DCD Heart Transplanted Recipient Population Only)

Serious Adverse Events (SAEs) and Heart Graft-related Serious Adverse Events (HGRSAEs) will be collected within the first 30 days post-transplant and the mean number of HGRSAEs per subject will be summarized using descriptive statistics. HGRSAEs are defined as the following adverse events (at most one per type): Moderate or Severe heart PGD (left or right ventricle) (not including rejection or cardiac tamponade) according to ISHLT consensus manuscript (as defined in Appendix 1) and primary graft failure requiring retransplantation.

SAEs and HGRSAEs will also be tabulated using counts and percentages alone and in regards to the relationship of the HGRSAE to the device, and the severity of the HGRSAE.

10.5. Sample Size Determination

We have assumed that transplantation of a DCD donor heart will occur at the same ratio as SOC heart transplants, despite the 3:1 randomization of ***DCD Heart Possible*** to ***SOC Heart Only***. The sample size calculations are based on the following specifications:

- Non-inferiority study with comparison of DCD heart transplanted recipients to SOC heart transplanted recipients
- Primary endpoint is patient survival at 6 months post-transplant
- One-sided normal approximation test

- Alpha = 0.05
- Power = 80%
- Assume 1:1 occurrence of SOC heart transplants (SOC1 and SOC2) and DCD heart transplants
- True SOC survival percentage = 93%
- True DCD survival percentage = 85%
- Non-inferiority margin = 20%.

Based on these assumptions, a sample size of 84 DCD heart transplanted recipients and at least 84 SOC heart transplanted recipients will provide at least 80% power.

This sample size was increased to 90 per group to reflect subjects who are lost to follow-up, withdraw or do not meet eligibility criteria.

To ensure timely completion of the trial, TransMedics proposes the following modification to the enrollment of SOC subjects:

1. As soon as 90 DCD recipients are transplanted, the trial enrollment will stop, regardless of the number of SOC transplanted recipients.
2. If, at the time the 90^{h} DCD recipient is transplanted, the SOC enrollment is less than the proposed 90 subjects, the outcomes for the remaining subjects will be obtained from the UNOS registry by accessing patient and graft demographics and survival data for SOC subjects transplanted at the participating Heart DCD trial investigational sites over the previous 2 years. The distribution of SOC subjects obtained from UNOS will reflect the distribution of enrollment in the Heart DCD among the various sites.
3. The final SOC1 and SOC2 patient cohorts will include the subjects transplanted in the trial, supplemented with subjects obtained from UNOS at the same investigational sites, to reach the SOC sample size of 90 subjects.

11. 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.

11.1. 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 not associated with the OCS Heart System such as graft failure, primary graft dysfunction, rejection, infection and other organs/systems complications, graft vessel disease (an expression of chronic rejection), abnormal kidney function, diabetes, high level of cholesterol, high blood pressure, cancer and neurological complications.

- **The Potential Risks Associated with OCS Heart System:** Subjects have the risk of not receiving organs preserved with the OCS Heart System under certain conditions including: (1) the OCS Heart System may not work properly, or there may not be personnel available trained in the use of the Heart System or (2) the OCS Heart System may malfunction, or the medical staff may make an error which could lead to damage of the donor heart. If this occurs, the subject will have to wait for a new donor heart to become available. 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. It is also possible that the donor heart may not meet transplantability criteria after OCS preservation and would be turned down for transplant. In the EXPAND trial and in trials of DCD donors conducted outside the U.S., only 20% of the donor hearts were turned down following OCS preservation so the anticipated frequency of this event is low.

11.2. 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 OCS has undergone extensive preclinical and animal studies to demonstrate that the device performs as intended and all materials are biocompatible. Previous clinical studies, including the Heart EXPAND trial and studies of DCD hearts performed outside the U.S., have not indicated any safety signals that would preclude initiation of this study.

In addition, 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 are 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 accepted for transplantation. The recipient should not be subjected to any surgical or medical procedures until the heart has been accepted for transplantation by the transplanting team.
- As with any heart transplant procedure, subjects will be monitored before, during and after the operative procedure. The investigators have extensive experience with heart transplants and will be trained to use the OCS Heart System to further minimize risk.
- 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.

11.3. 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 that approximately 25% of the patients on the national waiting list have either died or their health deteriorated prior to a heart transplant procedure.

The OCS Heart System's preservation and assessment capabilities could potentially increase the rate of utilization of donor hearts that are not used due to the limitations of cold storage techniques. The previous Heart EXPAND study demonstrated an 80% utilization of these expanded criteria donor hearts, and studies of the OCS performed outside the U.S. observed 78 - 80% utilization of DCD hearts. This could improve the chances of waiting list recipients to receive a lifesaving heart transplant and reduce waiting list time and mortality. In addition, the OCS heart's ability to assess donor hearts after removal allows for the assessment the function of the donor heart before it is transplanted.

11.4. Risks Benefit 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 the potential risks to trial subjects.

12. DEVICE/SITE MANAGEMENT

12.1. 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 only.

The OCS and its components will be clearly labeled as an investigational device according to 21 CFR 812.5. The labeling provides instructions for use for the device. A copy of the Instructions for Use will be provided to each investigational site.

12.2. Storage

The investigational devices will be stored in a secure location. 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. 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%).

12.3. Accountability

The investigator or designee will maintain a record of investigational devices received, used, discarded, or returned to the Sponsor.

12.4. 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.

13. 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.

13.1. Institutional Review Boards (IRB)

Prior to initiation of any trial procedures, trial documents will be submitted to each site's IRB 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. 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.

13.2. Informed Consent

The IRB 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 in Appendix 3.

14. DATA COLLECTION/RECORDS/REPORTS

14.1. Investigator Records

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

- Signed Investigator Agreement
- Signed financial disclosure form
- Curriculum Vitae (CV).

Written approval of the protocol and informed consent document from the IRB; Investigators will be responsible to maintain on file the following records (Note that this is not the complete list of items to be maintained):

- All relevant correspondences and required reports that pertain to the trial
- Records of receipt, use or disposition of the investigational device
- 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.

14.2. 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 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 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 at regular intervals but at least on an annual basis.
- The investigator will notify the Sponsor and the IRB 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 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. 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 the Sponsor.

14.3. Data Collection

All data required by the trial protocol will be entered into the trial database by the investigator or his or her designate. A copy of draft eCRFs is provided in Appendix 4.

14.4. Source Documents

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

During monitoring visits, source documents will be reviewed to ensure accuracy and validity of data recorded on the CRFs. Source document verification will be performed by TransMedics or its designee, with due regard to subject confidentiality.

14.5. 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.

15. CLINICAL MONITORING

15.1. Monitoring

The trial will be monitored by TransMedics. All monitors will be qualified by education, training, and experience. After the study has been initiated, TransMedics or its designee will perform periodic monitoring visits to assess study progress, perform device accountability, assess the adequacy of records, and to ensure adherence to the study protocol. Monitoring visits could be done live or via webconference.

A summary of the monitoring visit, including documentation of completed previous action items and/or new or outstanding action items, and/or significant findings will be provided to the Investigator.

In addition to periodic monitoring visits, TransMedics may perform remote monitoring to ensure data are submitted in a timely manner. Ongoing communication with investigators and study staff will be performed through written correspondence and telephone conversations.

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

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's general monitoring procedures for investigational studies are described below.

15.2. Site Initiation Visit

TransMedics or its designee will be responsible for determining and documenting that each investigator clearly understands and accepts the responsibilities and obligations incurred in conducting a clinical study. The sponsor or its designee will ensure, prior to study initiation, that the investigator:

- Understands the requirements for device accountability
- Understands the requirements of the clinical protocol
- Understands reporting obligations
- Understands and accepts the obligations to obtain informed consent
- Understands and accepts the obligation to obtain Institutional Review Board approval of the protocol and informed consent form prior to the enrollment of the first subject.
- Has adequate facilities to conduct the investigation.

Site initiation could be done via webconference.

15.3. Periodic Monitoring Visits

Monitoring visits will be conducted as scheduled by the sponsor. The monitor should visit (or conduct the visit via webconference) with 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 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 and Sponsor.
- The appropriate staff is carrying out trial activities.

15.4. 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.

15.5. Study Close-out Visit

The study close-out visit may be combined with a monitoring visit. The following tasks will be completed at close-out visit.

- Ensure that all required CRFs have been completed/submitted.
- Ensure final disposition of investigational devices.
- Remind the investigator of the obligation to retain the records in accordance with local country requirements, and prepare a final report for the sponsor and Institutional Review Board.

15.6. Protocol Deviations

The study should be conducted as described in this protocol. All deviations from the protocol should be reported to the Sponsor by entering a protocol deviation form into the study database.

For sites who demonstrate repeated deviations that may affect the safety of subjects, and/or the integrity of the data, corrective measures will be instituted such as re-training. Continued protocol deviations may result in the site's termination from the trial.

15.7. Clinical Events Committee (CEC)

The Sponsor will utilize an independent Clinical Events Committee (CEC) to provide individual serious adverse event adjudication for the trial. It is anticipated that the CEC will meet with the Sponsor on a periodic basis, or as needed, depending on the rate of patient accrual. The CEC will be guided by the CEC Charter; however, the primary responsibilities of the CEC are to:

- Review reportable serious adverse events, including PGD, that occur over the course of the trial and the subsequent classification of these adverse events as related to the device.
- Provide recommendations to extend the length of follow-up past 30 days post-transplant for a subject experiencing a serious adverse event.

15.8. 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 3 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 word "Stop" in a cell indicates that the study would be stopped if this condition were met. If the word "Continue" 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 3: Conditions under which Study Would be Stopped

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

TransMedics will be responsible for implementing the stopping rule.

15.9. Investigator Training

Device, protocol and electronic database training will be provided to the appropriate personnel 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.

16. 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.

17. 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. Protocol amendments will be submitted to

the chairman of the IRB responsible for reviewing amendments. Except for "administrative letters," investigators will await IRB approval of protocol amendments before implementing the change(s).

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APPENDIX 1. ISHLT CONSENSUS MANUSCRIPT HEART PRIMARY GRAFT DYSFUNCTION (PGD) (KOBASHIGAWA, ET AL., 2014)

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 ≤ 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 ≤ 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.

Note: All incidences of PGD will be adjudicated by the CEC.

Hemodynamic data will be used in the assessment of PGD severity only if collected by centers as clinically indicated, per the institution's standard of care. This approach is consistent with contemporary U.S. publications on PGD using ISHLT criteria (Nicoara, et al., 2018; Squiers, et al., 2018). If hemodynamic data are not collected, the CEC will use available clinical data to adjudicate PGD severity grading.

APPENDIX 2. 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	X	
OCS Preservation Parameters		X
OCS Lactate Levels		X
Device Malfunction (if applicable)		X
Non-transplant Reasons (if applicable)		X

Evaluations	DCD Transplanted Recipient Schedule of Assessments							
	Day of Tx	T0[a]	T24	T72	Initial Hospital Discharge	Day 30	Mo 6[c]	Mo 12[d]
Eligibility & Informed Consent	X							
Demographics/ Characteristics	X							
Medical & Cardiac History	X							
Transplant Details	X							
PGD Scores			X					
Inotropic Support		X	X					
Right Heart Catheter Results		X[b]	X[b]					
Mechanical Circulatory Support		X	X	X				
Patient & Graft Survival		X	X	X	X	X	X	X
Echocardiogram			X					
Initial ICU Stay					X			
Initial Hospital Stay					X			
HGRSAEs and SAEs	X	X	X	X		X		
Cardiac Allograft Vasculopathy								X[b]

a T0 is defined as the time of initial admission to ICU immediately post-heart transplant procedure

b ONLY Tests regularly scheduled per center standard of care or performed due to a clinical cause at these timepoints will be collected.

c Six month follow-up window is ± 30 days

d Twelve month follow-up window is ± 60 days

APPENDIX 3. DRAFT PATIENT INFORMED CONSENT FORM TEMPLATE

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APPENDIX 4. DRAFT ELECTRONIC CASE REPORT FORMS

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