INVESTIGATIONAL PLAN/PROTOCOL

Continued Access Protocol to collect additional evidence to evaluate the Safety and Effectiveness of The Portable Organ Care System (OCS™) Heart For Preserving and Assessing Expanded Criteria Donor Hearts for Transplantation (Heart EXPAND CAP)

Number OCS-CAR-121918

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CONFIDENTIAL – PROPRIETARY INFORMATION

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OCS™ HEART EXPAND CAP SYNOPSIS

Protocol Title	Continued Access Protocol to collect additional evidence to evaluate the Safety and Effectiveness of The Portable Organ Care System (OCS™) Heart for preserving, resuscitating and assessing Expanded Criteria Donor Hearts for Transplantation (Heart EXPAND CAP)
Intended Use	The OCS™ Heart will be used to preserve and assess donor hearts that do not meet current standard donor heart acceptance criteria for transplantation for one or more of the following reasons: • Expected total cross-clamp time of ≥4 hours; • Expected total cross-clamp time of ≥2 hours **PLUS** one or more of the following risk factors: – Donor age 45-55 years, inclusive, with no coronary catheterization data; or – Donor age ≥55 years; or – Left ventricular septal or posterior wall thickness of >12mm, but ≤16 mm; or – Reported down time of ≥20 min, with stable hemodynamics at time of final assessment; or – Left heart ejection fraction (EF) ≥40%, but ≤50% at time of acceptance of offer; or – Donor angiogram with luminal irregularities with no significant CAD (≤50%); or – History of carbon monoxide poisoning with good cardiac function at time of donor assessment; or – Social history of alcoholism with good cardiac function at time of donor assessment; or – History of diabetes without significant CAD (≤50%) on angiogram
Objectives	To provide additional data evaluating the safety and effectiveness of the OCS™ Heart System to preserve and assess donor hearts that do not meet current standard donor heart acceptance criteria (as identified above) for transplantation to potentially improve donor heart utilization for transplantation at a range of transplant centers in the U.S. and to permit patients and physicians access to the OCS Heart System while a PMA application is under preparation and review.
Trial Design	A prospective single-arm trial
Trial Size	A maximum of 8 participating sites with 75 transplanted heart recipients
Screening and Treatment	Donor hearts that are deemed acceptable for transplant will be screened for trial eligibility. Eligible donor hearts will be preserved and assessed with the Organ Care System (OCS). After OCS preservation and assessment, donor hearts will be evaluated for acceptability for transplantation according to prespecified criteria. Primary heart transplant candidates will be screened for trial eligibility. Every eligible candidate will be asked to participate. Eligible heart transplant candidates will receive OCS preserved donor hearts that have been deemed clinically acceptable for transplantation following preservation by the treating transplant clinical team according to specified criteria.
Donor Heart Eligibility Criteria	**Inclusion** At least one of the following: • Expected total cross-clamp time of ≥4 hours; • Expected total cross-clamp time of ≥2 hours **PLUS** one or more of the following risk factors: – Donor age 45-55 years, inclusive, with no coronary catheterization data; or – Donor age ≥55 years; or – Left ventricular septal or posterior wall thickness of >12 mm, but ≤16 mm; or

	– Reported down time of ≥20 min, with stable hemodynamics at time of final assessment; or – Left heart ejection fraction (EF) ≥40%, but ≤50% at time of acceptance of offer; or – Donor angiogram with luminal irregularities with no significant CAD (≤50%); or – History of carbon monoxide poisoning with good cardiac function at time of donor assessment; or – Social history of alcoholism with good cardiac function at time of donor assessment; or – History of diabetes without significant CAD (≤50%) on angiogram. **Exclusion** • CAD with >50% stenosis on angiogram, or • Cardiogenic shock or myocardial infarction, or • EF consistently <40%, or • Significant valve disease except for competent bicuspid aortic valve.
Recipient Eligibility Criteria	**Inclusion** • Registered primary heart transplant candidate • Age ≥18 years old • Written informed consent. **Exclusion** • Prior solid organ or bone marrow transplant • Chronic use of hemodialysis or renal replacement therapy for diagnosis of chronic renal insufficiency requiring dialysis • Multi-organ transplant.
Donor Heart OCS Acceptance and Rejection Criteria	**Accept for Transplantation** 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). Parameters should be maintained within the following ranges for acceptance: • Final arterial perfusate lactate <5 mmol/L with stable lactate trend • Stability of OCS Heart Perfusion Parameter trends over time within the guidance ranges below: – Aortic Pressure (mean AOP): 40-100 mmHg – Coronary Flow (CF): 400-900 mL/min. **Reject for Transplantation** Donor hearts preserved on the OCS will be rejected for any of the following: • Transplanting surgeon and/or designee is clinically unsatisfied with donor heart condition/performance on the OCS Heart System at final evaluation, e.g., unstable and rising arterial lactate despite multiple maneuvers to optimize perfusion parameters (increasing AOP and/or CF) • Final arterial perfusate lactate ≥5 mmol/L 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.
Primary Endpoint	• A composite of patient survival at Day 30 and absence of severe primary heart graft dysfunction (PGD) (LV or RV) in the first 24 hours post-transplantation according to ISHLT consensus manuscript (as defined in Appendix 1 of protocol)

Secondary Endpoints	• Patient and graft survival at Day-30 post-transplant • Incidence of severe primary heart graft dysfunction (PGD) (LV or RV) in the first 24 hours post-transplantation according to ISHLT consensus manuscript (as defined in Appendix 1 of protocol) • Rate of donor heart utilization, defined as the proportion of eligible donor hearts that were successfully transplanted after preservation and assessment on the OCS Heart System.
Other Endpoints	• Patient survival at 6 and 12 months post-transplant • Incidence of primary graft failure requiring re-transplantation through 12 months post-transplant • Duration of initial post-transplant ICU stay • Duration of initial post-transplant hospital stay.
Safety	Incidence of heart graft-related Serious Adverse Events (HGRSAEs) in the first 30 days post heart transplantation, defined as: • Moderate or Severe primary heart graft dysfunction (PGD) (left or right ventricle) (not including rejection or cardiac tamponade) according to ISHLT consensus manuscript (as defined in Appendix 1 of the protocol). • Primary graft failure requiring re-transplantation.
Follow-up	All patients will be followed for 12 months post-transplant (including post-market).
Statistical Methods	The transplanted recipient population will consist of all recipients who are transplanted according to this protocol. The analyses of all effectiveness and safety endpoints, except the rate of donor heart utilization, will be based on the transplanted recipient population. The OCS heart population will consist of all donor hearts that are instrumented on the OCS Heart System. The analysis of the rate of donor heart utilization that were successfully transplanted after preservation and assessment on the OCS Heart System will be based on the OCS heart population. The primary endpoint will be summarized using counts and percentages and an exact 95% confidence interval for the true percentage based on the binomial distribution. Each secondary effectiveness endpoint will be summarized using counts and percentages and an exact 95% confidence interval for the true percentage based on the binomial distribution. The first two secondary effectiveness endpoints will be analyzed using the transplanted recipient population. The rate of donor hearts that were successfully transplanted after preservation and assessment on the OCS Heart System (i.e., donor heart utilization), will be analyzed using the OCS heart population. Safety will be analyzed principally by examination of the frequency of adverse events. In particular, the number of heart graft-related serious adverse events (HGRSAEs) up to the 30-day follow-up after transplantation per subject will be analyzed. This endpoint is defined to consist of the following adverse events (at most one per type), if they are serious adverse events: • Moderate or severe primary heart graft dysfunction (PGD) (left or right ventricle) (not including rejection or cardiac tamponade) according to ISHLT consensus manuscript (as defined in Appendix 1 of the protocol). • Primary graft failure requiring re-transplantation.

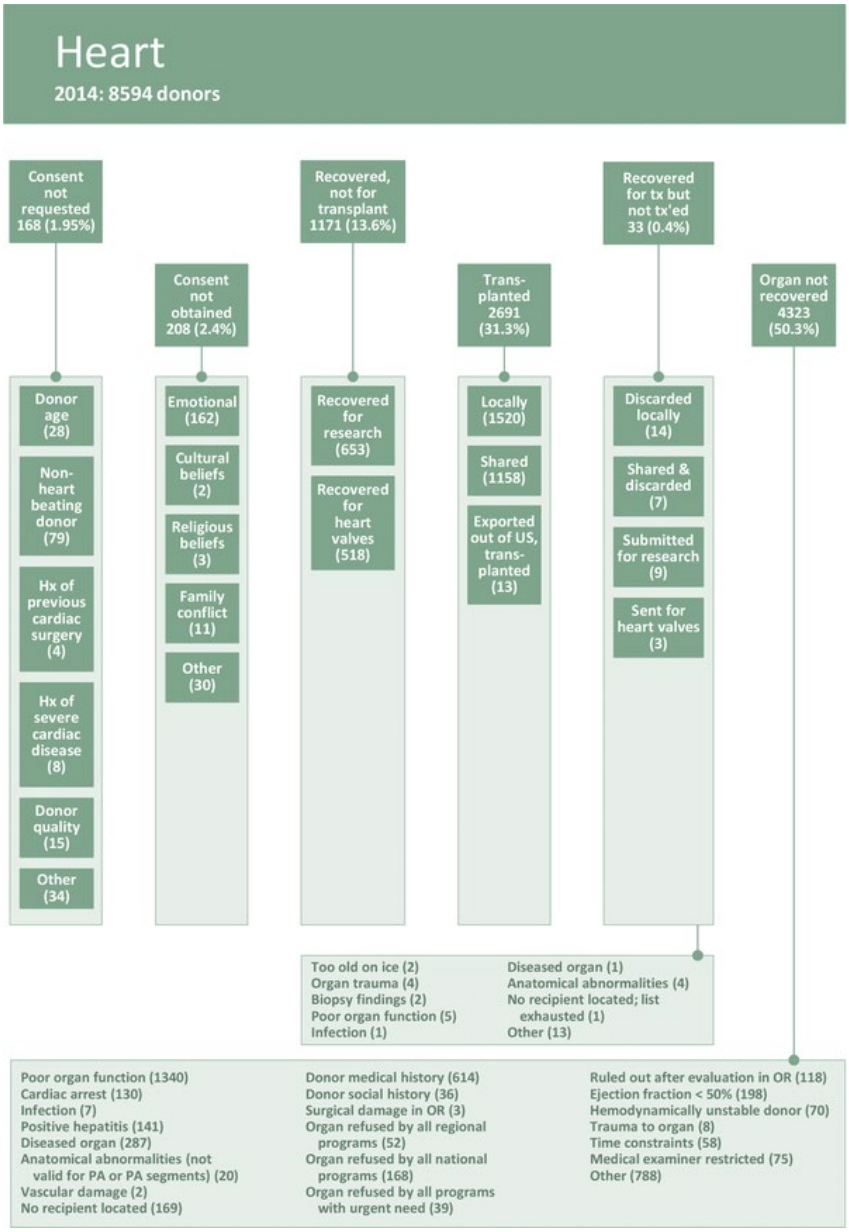
	This endpoint will be summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum, maximum, and a 95% confidence interval for the mean based on the t-distribution.
Determination of Sample Size	This is a continued access protocol and does not have a statistically determined sample size
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

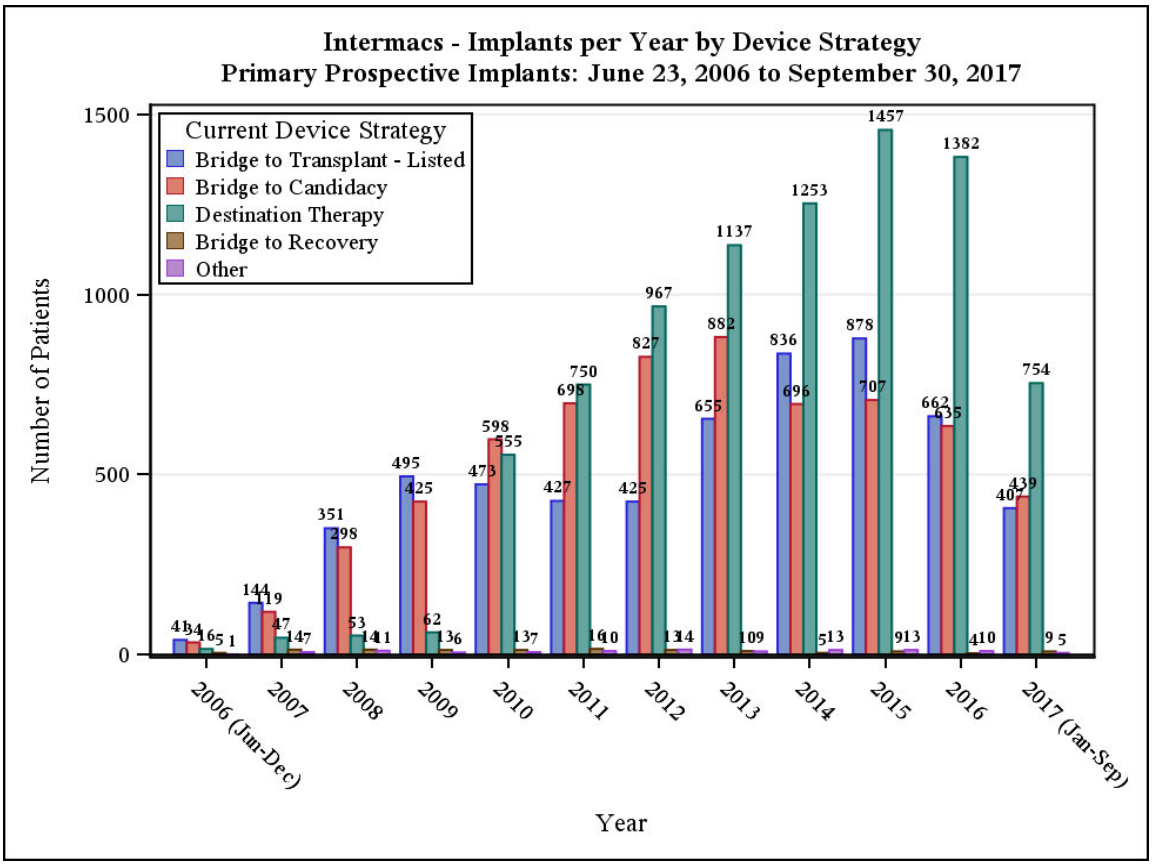
Heart transplantation is the gold standard and the most cost-effective treatment for end-stage heart failure (Hunt and Haddad 2008). While the demand for heart transplantation globally has increased significantly each year, the utilization or recovery of available donor hearts for transplantation has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

Figure 1: Heart Organ Use in the United States 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 (so-called "Destination Therapy") (Figure 2).

Figure 2: MCS devices implanted in US 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 US 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 (see Table 1). Status 1A patient 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.

The OCS Heart System addresses these challenges by expanding the donor pool and allowing life-saving heart transplantation to become available to more recipients. Currently, the OCS Heart System technology is the only portable system available for ex-vivo maintenance of the donor heart in a metabolically active and beating state. It enables the donor heart to be maintained in a near physiologic functioning state ex-vivo, continuously perfused with a warm oxygenated and nutrient-enriched blood perfusate. Specifically, the OCS Heart System offers the following advantages and capabilities:

- Resuscitation of the extended criteria 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 minimizing the risk of transplanting poorly functioning 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 utilizing extended criteria donors with the OCS Heart System has the potential to provide them 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. OCS Heart EXPAND Trial

The Heart EXPAND trial (G140111) is an FDA-approved single arm study of extended criteria donor hearts, i.e., those that are currently not transplanted or are seldom transplanted in the U.S. due to challenging donor characteristics/medical history, or projected extended ischemia times (possibly due to procurement or complicated recipient explantation issues due to VADs).

The Heart EXPAND trial was designed to enroll 75 subjects at a maximum of 20 U.S. sites. The primary endpoint is a composite of patient survival at Day 30 post-transplant and absence of severe primary graft dysfunction (PGD) at 24 hours post-transplant. Secondary Endpoints included: donor heart utilization rate (i.e., how many of these non-standard hearts were actually transplanted after OCS Heart System preservation and assessment), 30-day patient survival and freedom from severe primary graft dysfunction (PGD) at 24 hours after transplant.

The 75th subject was enrolled on March 25, 2018, and the trial has reached its enrollment limit. The trial data are still being entered, cleaned and adjudicated, and patient follow-up is on-going. The sections below summarize the available data to date.

2.2.1. Donor Heart Utilization

The Heart EXPAND trial was designed for 75 subjects at 20 US sites. The primary effectiveness endpoint is a composite of patient survival at Day 30 post-transplant and freedom from severe primary graft dysfunction (PGD) at 24 hours post-transplant. Secondary endpoints include: donor heart utilization rate (i.e., how many of these non-standard hearts were actually transplanted after OCS Heart System preservation and assessment), 30-day survival and freedom from severe PGD at 24 hours after transplant. The primary hypothesis for this trial is that the true proportion of transplanted recipients with the composite of patient survival at Day 30 post-transplantation and freedom from severe PGD in the first 24 hours post-transplantation is greater than the Performance Goal value of 0.65 (65%). This performance goal is based on literature and statistics for standard criteria heart transplants. Prior to the Heart EXPAND trial, there were no data available on post-transplant outcomes of extended criteria donor hearts.

The safety endpoint is the number of heart graft-related serious adverse events (HGRSAEs) up to the 30-day follow-up after transplantation per subject. The endpoint is defined to consist of the following adverse events (at most one per type) if they are serious adverse events:

- Moderate or severe primary heart graft dysfunction (PGD) (left or right ventricle) (not including rejection or cardiac tamponade) as defined in Appendix 2 of the protocol, according to the ISHLT consensus manuscript.
- Primary graft failure requiring re-transplantation

The Heart EXPAND trial is a single arm study of extended criteria donor hearts, i.e., those that are currently not transplanted or are seldom transplanted in the US. To be included in this study, donor hearts had to have met one or more of the following inclusion criteria:

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

TransMedics currently has reached the enrollment limit of 75 subjects in the Heart EXPAND trial. The data are still being entered, verified, adjudicated and analyzed, but the section below summarizes the available data as of September 2018.

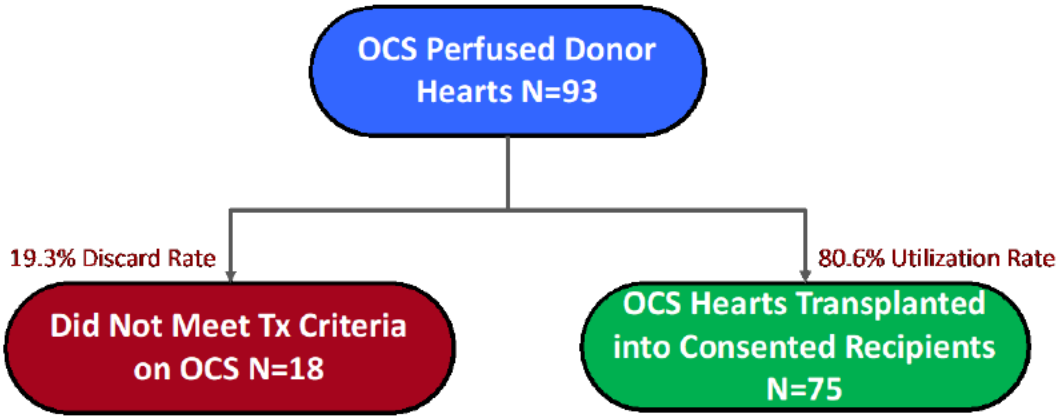
2.2.2. OCS Heart EXPAND Trial –Subject Disposition

The 75th subject was enrolled on March 25, 2018, and the trial has reached its enrollment limit.

2.2.3. Donor Heart Utilization

In the Heart EXPAND trial, a total of 93 donor hearts were preserved and assessed on OCS and of these, 75 were transplanted, giving a utilization rate of 80.6% (See Figure 3).

Figure 3: Heart EXPAND Donor Utilization



We believe that this is a clinically important result, given that donor hearts were rejected by other centers and would not have been utilized outside of the Heart EXPAND trial. Table 2 below shows the donor match run data available from UNOS for the 93 donor hearts preserved on the OCS Heart System for the Heart EXPAND trial. These 93 hearts were refused for transplant by other centers an average of 65.6 times (median 29) before acceptance into the trial.

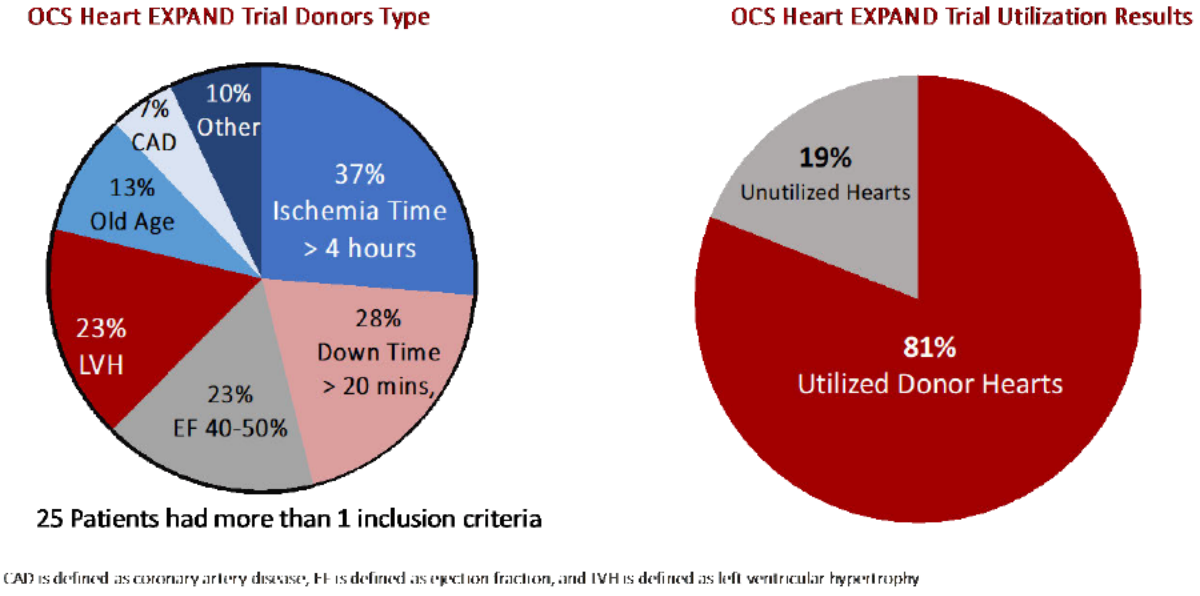
Table 2: Donor Heart Offers Refusals Prior to Acceptance in Heart EXPAND trial

	Donor Heart Offers from UNOS donor match run data N = 93
Mean number of Refusals per donor heart (Mean ± SD)	65.6 ± 89.6
Median number of Refusals per donor heart	29
Minimum - Maximum	0 - 379

2.2.4. Donor Demographics

Donors were included for various inclusion criteria as shown in Figure 4. Twenty-five of the 75 subjects (33%) met more than one inclusion criterion.

Figure 4: Donor Demographics in Heart EXPAND trial



CAD is defined as coronary artery disease, EF is defined as ejection fraction, and LVH is defined as left ventricular hypertrophy

2.2.5. Recipient Demographics

The recipient demographics are shown in Table 3 below. The majority of recipients (69.3%) were status 1A and were on mechanical circulatory support at the time of transplant (62.7%; 47/75). The majority of these recipients (61.3%; 46/75) were on LVADs. Recipient characteristics are also presented by known risk factors for heart transplant recipients (Sorabella, 2015; Trivedi, 2016).

Table 3: Recipient Demographics in Heart EXPAND Trial

Recipient Characteristics	OCS Transplanted Recipients N=75
Risk Factors	
Age > 65	19 (25.3%)
History of Mechanical Circulatory Support	47 (62.7%)
• LVAD	46 (61.3%)
• RVAD	0 (0%)
• BiVAD	1 (1.3%)
• ECMO	0 (0%)
Female donor to male recipient mismatch	12 (16.0%)

Recipient Characteristics	OCS Transplanted Recipients N=75
Renal dysfunction	11 (14.7%)
Other Characteristics	
Age (years) mean ± SD	55.5 ± 12.6
Gender – male n (%)	61 (81.3 %)
BMI (kg/m^2) – mean ± SD	27.7 ± 4.7
Status n (%):	
• Status 1A	52 (69.3)
• Status 1B	22 (29.3%)
• Status 2	1 (1.3%)
Primary Etiology of Heart Failure Diagnosis	
• Ischemic Cardiomyopathy	26 (34.7%)
• Congenital Heart Disease	2 (2.7%)
• Restrictive Cardiomyopathy	7 (9.3%)
• Other	40 (53.3%)
%PRA mean (range)	7.9 (0-81)

2.2.6. Heart EXPAND Trial Results – Patient Survival

All subjects have reached the primary endpoint time point of 30-days and the follow-up timepoint of 6 months. Follow-up at 12 months is still on-going. Survival is shown in Table 4 below. At 30 days post-transplant, survival was 94.7% and at 6 months, survival was 88%.

Table 4: Summary of available survival data for subjects in OCS Heart EXPAND trial

	Survival OCS Heart EXPAND N=75
30 days (% n/N)	94.7% (71/75)
Hospital Discharge (%, n/N)	92.0% (69/75)
6 months (%, n/N)	88.0% (66/75)

As of the date of this report, 12-month follow-up is available for 40 of the 75 enrolled subjects. Two additional patients died between 6 and 12 months.

2.2.7. Heart EXPAND Trial Results – Primary Graft Dysfunction (PGD) and Heart Graft-Related Serious Adverse Events (HGRSAEs)

The second component of the primary endpoint, severe Primary Graft Dysfunction (PGD) at 24 hours, is shown in Table 5 below. There was a 10.7% (8/75) incidence of severe PGD following transplant for the Heart EXPAND subjects.

Table 5: Severe PGD in the first 24 Hours for Heart EXPAND Subjects

Adjudicated Primary Graft Dysfunction	OCS Heart EXPAND N=75
Severe PGD	10.7% (8/75)
PGD-LV with implantation of ECMO	8.0% (6/75)
PGD-RV with implantation of RVAD	2.7% (2/75)

The incidence of moderate or severe PGD within 30 days of follow-up was 12.0% (9/75). One patient (1.3%) had primary graft failure requiring re-transplantation.

Both the incidence of severe PGD within 24 hours and the incidence of moderate and severe PGD within 30 days after transplant observed in the Heart EXPAND trial were comparable to, or in some cases, substantially less than the values reported in the literature, which ranged from 13% to 36% (Dronavalli, et al., 2013; D'Alessandro et al., 2011; Lima et al., 2006), including more recent studies which utilized the ISHLT criteria (Nicoara, et al. 2018; Singh et al., 2018; Sabatino et al., 2017; Squiers, et al., 2017).

2.2.8. Summary of Heart EXPAND Trial Results to Date

Although the data for Heart EXPAND trial are still being collected, monitored, adjudicated and analyzed, the preliminary results are encouraging, demonstrating:

- Utilization rate of 80% of donor hearts that are seldom 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% were transplanted successfully in this study.
- The incidence of ISHLT severe PGD within 24 hours was 10.7%, and the incidence of ISHLT moderate and severe PGD within 30 days post-transplant was 12.0%. These rates compare favorably with contemporary literature reporting PGD rates post-heart transplantation using the ISHLT criteria.
- Survival at 30 days and 6 months was 94.7% and 88%, respectively, with 12 month follow-up still on-going.

2.3. OCS Heart PROCEED II Trial

The PROCEED II Trial, conducted under approved IDE application G060127, was a randomized, prospective, open-label multi-center, clinical trial that compared the safety and effectiveness of the OCS to cold storage standard of care for donor heart preservation (Control). The PROCEED II Trial was designed to test whether the clinical outcomes of patients undergoing heart transplantation with

standard donor hearts preserved on OCS were non-inferior to the outcomes of heart transplant recipients whose donor hearts were preserved using standard of care cold storage.

TransMedics received full approval for the PROCEED II trial protocol under IDE G060127/S024 on July 22, 2008. The results have been published in the Lancet (Ardehali, et al. 2015).

2.3.1. Study Purpose

The purpose of this trial was to compare the safety and effectiveness of the OCS Heart System to the standard of care cold storage (Control) for the preservation of standard donor hearts. The clinical trial and planned statistical analyses were a non-inferiority design intended to show that the OCS Heart System (OCS) was as safe and effective as cold storage for standard criteria heart preservation for transplantation.

2.3.2. Primary Study Endpoint

The primary study endpoint was 30-day patient survival following transplantation with the originally transplanted heart and no mechanical circulatory assist device at Day 30.

2.3.3. Secondary Study Endpoints

The secondary study endpoints were:

- Incidence of serious cardiac (graft) related adverse events, defined as those which are attributed to preservation injury of the donor heart in the first 30 days post-transplant: right ventricular dysfunction; left ventricular dysfunction; graft failure and myocardial infarction.
- Incidence of biopsy proven ISHLT grade 2R (moderate) or 3R (severe) acute rejection on any of the surveillance endomyocardial biopsies as determined by the core pathology laboratory or clinically symptomatic rejection requiring augmentation of immunosuppressive therapy during the 30-day follow-up period; and
- Length of intensive care unit (ICU) stay.

2.3.4. Subject Disposition

Of the 143 initially screened and randomized patients, 13 patients failed secondary screening/eligibility. Thus, 130 patients comprised the ITT Population, with 67 patients randomly assigned to the OCS Group and 63 patients randomly assigned to the standard cold storage group (Control Group). The As-Treated Population consisted of 128 randomized patients who received an OCS or Control donor heart, regardless of whether or not there was conformance with the randomization assignment, with 62 in the OCS Group and 66 is the Control group. The Per-Protocol Population comprised 121 randomized subjects who received a donor heart in conformance with the randomization assignment and had no major protocol violations, with 60 in the OCS Group and 61 in the Control Group.

2.3.5. Primary Study Endpoint Results

The study met its primary endpoint for all study populations, demonstrating that the OCS is non-inferior to Control preservation (Table 6).

Table 6: PROCEED II Primary Endpoint (30-Day Patient and Graft Survival and absence of a mechanical assist device at Day 30) for Various Study Populations

Study Populations	OCS Group	Control Group	Between Group Difference in %	95% Upper Confidence Bound for Difference in %	p-value*
Per Protocol	56/60 (93.3)	59/61 (96.7)	3.4	9.9	0.0469
As Treated	58/62 (93.5)	64/66 (97.0)	3.5	9.6	0.0404
Intent to Treat[1]	63/67 (94.0)	61/63 (96.8)	2.8	8.8	0.0239

Data are number (%).
The non-inferiority hypothesis was demonstrated for all three analysis populations as the 95% UCB for the difference between the two trial groups was <10% for all populations.
[1] Missing values were imputed with multiple imputation. The logistic regression method of imputation was used with terms for treatment, age, and gender.

There were 4 patients in the OCS group and 2 in the Control group who did not meet the primary endpoint due to death prior to 30-days post-transplantation. (No patient in either treatment group required a mechanical assist device at Day 30 post-transplantation.) The CEC-adjudicated causes of death did not appear to be related to the quality of the preservation of the donor heart.

2.3.6. PROCEED II Secondary Endpoint Results – Cardiac-Graft Related Serious Adverse Events – Principal Safety Measure

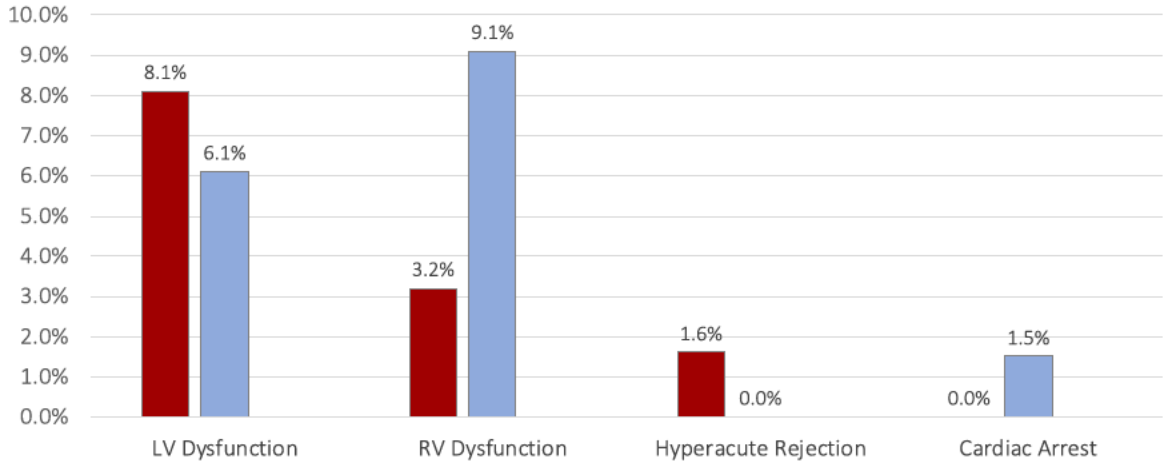
The study met the secondary endpoint of cardiac-graft related serious adverse events, demonstrating the safety of the OCS for donor heart preservation (non-inferiority of OCS compared with Control) (Table 7). All adverse events were reviewed by the CEC and adjudicated data are presented. Eight (8) OCS patients and 9 Control patients experienced one or more cardiac-graft related serious adverse events as shown in Figure 5. There was a trend in that 6 (9.1%) of Control patients experienced right ventricular dysfunction compared to 2 in the OCS Group (3.2%).

Table 7: Secondary Endpoint – Patients Experiencing At Least One Cardiac-Graft Related Serious Adverse Event (CEC-adjudicated)

Study Populations	OCS Group (N=62)	Control Group (N=66)	Between Group Difference in %	95% Upper Confidence Bound for Difference in %	p-value*
As Treated	8/62 (12.9)	9/66 (13.6)	0.7	9.1	0.0368

Data are number (%).
*The non-inferiority hypothesis was demonstrated as the 95% UCB for the difference between the two trial groups was <10%.

Figure 5: Cardiac Graft Related Serious Adverse Events for OCS (red) and Control (blue) in PROCEED II Study (As Treated Population)



2.3.7. Mechanical/Circulatory Support Following Transplant

Following transplantation, 9 OCS and 7 Control patients required mechanical circulatory support (MCS) during the 30 days post-transplantation although no patient required such support at day 30. The number of patients who recovered and were discharged alive post-MCS use was comparable between OCS and control.

2.3.8. Turned Down OCS Preserved Donor Hearts Based on OCS Assessment

During the conduct of Heart PROCEED II trial, five donor hearts (for four patients) treated with OCS preservation were deemed not acceptable for transplantation while on the OCS and were turned down. These four patients were subsequently transplanted with another donor heart offer and their outcomes were included in the analysis of this trial. Four (4) of the 5 donor hearts were declined due to rising perfusate lactate levels during the OCS preservation session, indicating persistent myocardial ischemia despite attempts to optimize myocardial perfusion. One heart was declined due to friable aortic tissue that made it difficult to support the aorta cannula for OCS perfusion.

2.3.9. Overall Adverse Events

The incidence of adverse events was similar between the OCS and Control groups, and there were no statistical differences between the two groups. Both treatment groups experienced a rate of adverse events slightly greater than 60% as expected given the invasive nature of heart transplantation procedures.

2.3.10. Summary Conclusions of PROCEED II Trial

- The study met its primary effectiveness endpoint, demonstrating that the OCS is non-inferior to SOC. The primary endpoint was met regardless of the study population analyzed –including the PP, ITT and AT populations.
- The incidence of cardiac- graft related serious adverse events (Cardiac Graft SAEs) in the OCS arm was shown to be non-inferior to the SOC arm. The use of cardiac-graft related SAEs is a

measure of post-transplantation graft function and directly reflects the quality of the preservation of the donor heart.

- During the conduct of the PROCEED II trial, five donor hearts designated for four randomized patients (1 patient with 2 donor hearts offered) were deemed not acceptable for transplantation while on the OCS and were declined for transplantation. The four patients (that these hearts were assigned to) were subsequently transplanted with another donor heart offer and their outcomes were included in the analysis of this trial. Four (4) of the 5 donor hearts were declined due to rising perfusate lactate levels during the OCS preservation session, indicating persistent myocardial ischemia despite attempts of optimization of myocardial perfusion and 1 heart was declined due to friable aortic tissue that was difficult to support the aorta cannula for OCS perfusion. The ex-vivo metabolic assessment afforded by OCS is a new capability that enables some biomarker data to be assessed by the transplant team up to the point of transplantation, which cannot be achieved with cold storage.

2.3.11. SRTR Database – Long Term Follow-up PROCEED II Patients

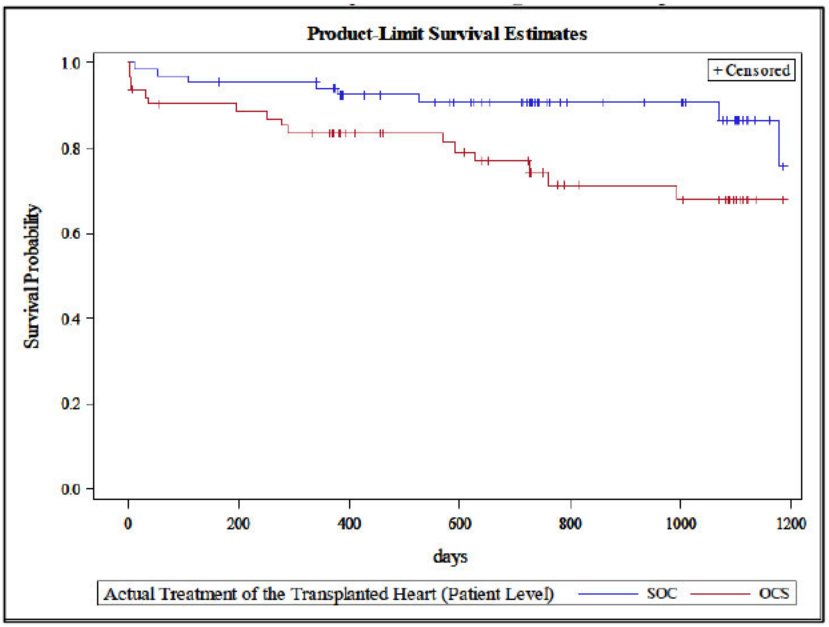
Although the PROCEED II trial was designed with a maximum 30-day follow-up, FDA requested longer term survival data and TransMedics obtained data for the PROCEED II subjects from the Scientific Registry of Transplant Recipients (SRTR) voluntary registry. The SRTR voluntary registry (http://www.srtr.org/) manages the collection of U.S. national transplant data and conducts research on solid-organ transplantation in the U.S.[1] In addition, TransMedics contacted its international sites to obtain long term follow-up on the 10 international patients who participated in the PROCEED II Trial since the SRTR patient registry includes only US patients. Finally, two US patients in the PROCEED II Trial were not included in the registry data set provided by SRTR (one due to transcription error in the UNOS ID number and one for unknown reasons). TransMedics contacted the US investigational sites and obtained follow-up status on these two US patients and survival status was confirmed. By aggregating the SRTR and site data, long-term follow-up information was available for patients ranging from 1 year up to 5 years post-transplantation.

Post-hoc observational survival analyses for the PROCEED II trial patients were performed with Kaplan-Meier survival estimates calculated separately for the OCS and standard of care (SOC) Groups. These analyses considered all-cause mortality from the time of transplantation through 3 years and 3 months, and included 130 patients (118 from the SRTR registry data set and 12 from TransMedics data collection directly from the investigational sites).

Figure 6 below shows the post-hoc observational Kaplan-Meier survival analyses for All-Cause Mortality, which included 16 deaths in the OCS Group and 8 deaths in the SOC Group from heart transplantation (Day 0) through the follow-up period (3 years and 3 months). There was an apparent decrease in survival for the OCS subjects compared to the SOC patients.

[1]The study used data from the SRTR. The SRTR data system includes data on all donor, wait-listed candidates and transplant recipients in the U.S., submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. The data reported here have been supplied by the Minneapolis Medical Research Foundation (MMRF) as the contractor for the Scientific Registry of Transplant Recipients (SRTR). The interpretation and reporting of these data are the responsibility of the sponsor and in no way should be seen as an official policy of or interpretation by the SRTR or the U.S. Government.

Figure 6: Kaplan-Meier Analyses for All-Cause Mortality for PROCEED II Trial Patients from the Time of Transplantation Through the Follow-up Period



A post-hoc observational analysis of all-cause mortality for the PROCEED II trial is shown in Table 8. The reported causes of death in both groups are consistent with the SRTR reported causes of deaths for adult heart transplant recipients in the U.S. (Colvin et al., OPTN/SRTR 2018, Annual Data Report). It is important to note that the long-term data were not collected as part of a pre-specified protocol, so patient care and clinical follow-up post-transplant were not standardized or recorded.

Table 8: Cause of Death for PROCEED II Patients

Cause of Death	OCS Group Number (%) (n=62)	Control Group Number (%) (n=68)
Primary Graft Failure (Non-immunological)	2 (3.2%)	3* (4.4%)
Graft Failure – Immunological	1* (1.6%)	1 (1.5%)
Unknown	1 (1.6%)	1 (1.5%)
Late Infection (>180 days post-transplant)	4 (6.5%)	1 (1.5%)
Malignancy	2 (3.2%)	1 (1.5%)
Multiple Organ Failure	3* (4.8%)	0 (0.0%)
Hemorrhage	2* (3.2%)	0 (0.0%)
Cerebrovascular	0 (0.0%)	1* (1.5%)
Protamine Reaction	1* (1.65%)	0 (0.0%)
Total Deaths	**16 (25.8%)**	**8 (11.7%)**

* 1 patient in each of these categories died within the primary 30-day follow-up and was analyzed in the primary effectiveness analysis.

2.3.11.1. Analysis of Cardiac Graft Related Deaths

TransMedics performed a post-hoc observational analysis of all cardiac-graft related deaths for the PROCEED II Trial patients using data collected from the above sources including the 30-day mortality from the PROCEED II trial, to assess the impact of preservation technologies on graft related mortality.

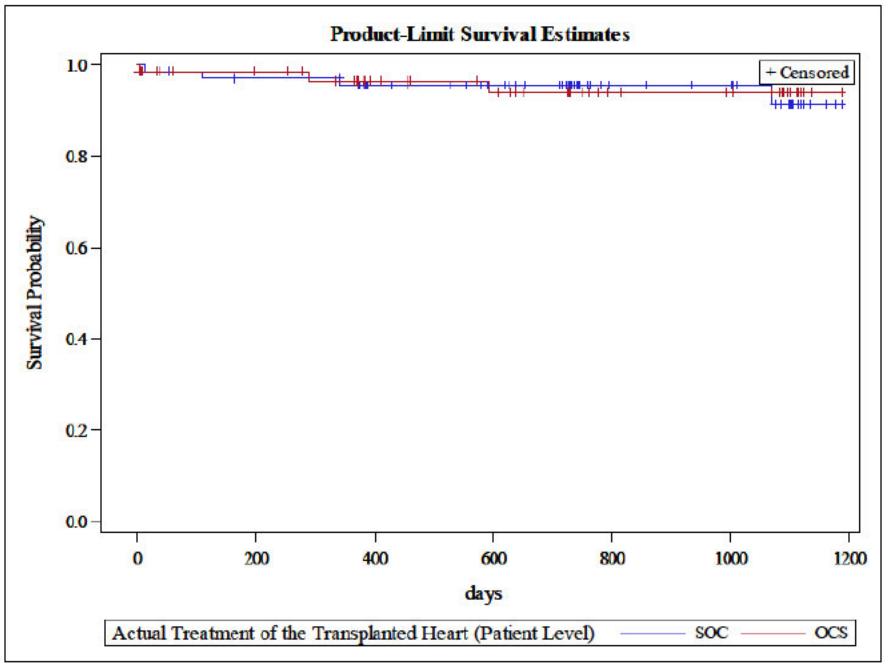
Table 9 and Figure 7 below represent the results of this analysis that included follow up through slightly over 3 years post heart transplant procedure. The number of patients whose cause of death was due to Primary Graft Failure (Non-immunologic or immunologic) was similar between the two groups (3 patients in the OCS Group and 4 in the Control Group). Graft failure is a leading cause of long-term mortality after adult heart transplantation as reported by the OPTN/SRTR causes of deaths for adult heart transplant recipients in the U.S. (Colvin, et al. 2018)

Table 9: Long Term Primary Graft Failure (Non-immunological) and Graft Failure – Immunological from PROCEED II Trial Patients

Cause of Death	OCS Group Number (%) (n=62)	Control Group Number (%) (n=68)
Primary Graft Failure (Non-immunological)[a]	2 (3.2%)	3 (4.4%)
Graft Failure – Immunological[b]	1 (1.6%)	1 (1.5%)
Total Graft Related Deaths	**3 (4.8%)**	**4 (5.9%)**

a: Any patient who had a cause of death identified as "Cardiovascular – Cardiac Arrest," "Graft Failure – Primary Failure," or "Primary Graft Dysfunction Causing Multiple Organ Failure" was classified as Primary Graft Failure (Non-Immunological) b: 1 patient died due to acute rejection and 1 patient died due to non-compliance.

Figure 7: Kaplan-Meier Analyses for Graft Failure Mortality for PROCEED II Trial Patients from the Time of Transplantation Through the Follow-up Period



2.3.11.2. Analysis of Other Causes of Death

There were 4 patients in the OCS Group whose cause of death was Late Infection (>180 days post-transplant); these patients died from a minimum of 197 days to a maximum of 727 days post-transplantation. As shown in Table 10 below, none of these patients had an infection SAE or AE in the 30-days following transplant, and therefore, it is most likely that the infections were not associated with the OCS preservation method, but rather with the immunosuppressed condition of these recipients. Please note that similar trends are reported in the SRTR patient registry in which infection is the leading cause of death within the first-year post-transplantation among adult heart recipients (Colvin et al., 2018).

Table 10: PROCEED II Patients with Cause of Death Late Infection

Subject ID	Arm	Cause of Death	Death Days Post-Tx	Infection AEs or SAEs ≤ 30Days
02-009	OCS	Viral Septicemia	571	No
02-035	OCS	Bacterial Septicemia	197	No
09-009	OCS	Viral Septicemia	727	No
11-033	OCS	Infection: Other	278	No
11-009	Control	Bacterial Septicemia	527	No

There were also 3 patients in the OCS Group who died of multiple organ failure; 1 patient died within 30-days from severe metabolic acidosis secondary to vasoplegia with good cardiac function and was analyzed in the primary effectiveness endpoint. Of the other 2 patients; 1 patient had a ventricular assist devices (VAD) pre-transplant. VAD use is a known risk factor for end-organ failure (i.e., kidney and liver). The other patient who died of Multiple Organ Failure had a history of chronic kidney disease, leukemia, hypothyroidism and severe pulmonary hypertension.

Three patients died of Malignancy (2 in OCS and 1 in Control) which is consistent with the SRTR reported causes of deaths for adult heart transplant recipients in the U.S.(Colvin, et al. 2018) and is often attributed to the immunosuppressed state of these recipients.

2.4. Long term follow-up from OCS Heart Studies conducted in the UK and Germany

The OCS Heart has been approved for broad clinical use in the EU and internationally and, therefore, has been used extensively in preserving donor hearts in variety of different clinical indications. Long term outcome data have been reported in peer reviewed scientific literature or have been available to the TransMedics from this experience. The following represents reported long-term follow-up data on 48 OCS Heart transplanted patients in two European centers.

A peer reviewed publication (Koerner et al., 2014) reported on 2-year survival data of OCS heart transplant recipients as compared to prospective, non-randomized, concurrent control patients transplanted with hearts preserved by cold static storage (CSS) in the same German institution. This study compared the long-term results of 29 heart transplant recipients who received OCS-preserved hearts to 130 heart transplant recipients who received hearts preserved using CSS at the same institution over the same period of time. All recipients received standard criteria donor hearts.

In this article, the authors summarized the key clinical outcomes at 30 days, 1 year and 2 years following heart transplantation. Table 11 below (taken directly from the publication) shows 1- and 2-year survival for OCS patients of 89%, compared to 1- and 2-year survival of 81% and 79% for the control patients.

Table 11: Overall Clinical Results from the Koerner et al Publication (Note that the Warm Blood Perfusion in this table refers to the OCS)

Table 4. Overall Clinical Results

Overall Clinical Results	Warm Blood Perfusion, (n = 29)	Cold Static Storage (n = 130)	P
Recipient survival after HTx, %			
30 Days	96	95	.39
1 Year	89	81	.24
2 Years	89	79	.19
Primary graft failure, %	6.89	15.3	.20
Severe acute rejection, %	17.2	23	.73
Hemodialysis, %	10	25.3	.05
In-hospital stay, mean (range), days	26 (20-108)	28 (19-143)	.80

Additional long-term data on a cohort of 19 OCS treated heart recipients and a concurrent control group of 24 cold storage heart recipients (Control) all treated at Papworth Hospital in the UK have been collected. Long term follow-up data were collected by Papworth Hospital staff, after Ethics Committee approval and waiver of informed consent (Tsui, 2015, unpublished data). The long-term survival results are shown in Table 12. These findings are similar to those observed in the Koerner et al. study in that the 1- and 2-year survival of OCS treated heart recipients was 89%, compared to 83% for the control group. All recipients received standard criteria donor hearts.

Table 12: Long Term Follow-up from a Cohort of OCS and Control Heart Transplant Recipients from Papworth Hospital

Survival Time	Kaplan-Meier Estimate of Survival Rate (%)	
	OCS (n=19)	CONTROL (n=24)
30 days	94.7%	87.5%
1 year	89.5%	83.3%
2 year	89.5%	83.3%

2.5. Discussion and Conclusions of the Long and Intermediate term Follow-up of OCS Heart System patients

When including long-term follow-up from SRTR and other sources, there were 16 deaths in the OCS Group and 8 deaths in the SOC Group in PROCEED II patients from Day 0 through the follow-up period (3 years and 3 months). There was an apparent decrease in survival for OCS patients compared to the SOC patients.

However, mirroring the short-term results of the PROCEED II trial, the SRTR long term data showed that the number of patients whose cause of death was due to PGF was similar between the two groups. The European data were consistent with this finding. Graft related mortality is the primary focus for assessing the impact of heart preservation technology such as the OCS Heart System.

All other causes of mortality observed were consistent with the SRTR reported long-term causes of deaths for adult heart transplant recipients in the U.S. and are likely related to the immunosuppressed condition and other clinical factors of the recipient.

2.6. Differences between PROCEED II and Heart EXPAND Trials

When considering the totality of the evidence supporting the safety of the OCS Heart System, it is important to recognize that the two previous IDE trials of the OCS Heart System present a number of key differences:

1. **Differences in Donors:** PROCEED II is a study of standard criteria donor hearts, while the Heart EXPAND trial is a study of extended criteria donor hearts, i.e., those that are seldom transplanted in clinical practice today.
2. **Differences in Recipients:** Subjects were enrolled in PROCEED II using different inclusion/exclusion criteria than Heart EXPAND. PROCEED II was designed in 2006, based on the publication of the pivotal clinical trial for Celsior, which was the only new device technology for donor heart preservation at that time (Vega, et al., 2001). Heart EXPAND, on the other hand, was designed in 2014 and reflects the current clinical practices in the treatment of heart failure (use of VADs) as well as contemporary practices in heart transplantation.
3. **Observed Cross Clamp Time vs Expected Cross Clamp Time:** Although expected cross clamp time $\geq$ 4 hours was the inclusion criteria for 37% of the donors in Heart EXPAND, and extended cross-clamp times were also observed in PROCEED II, there are fundamental differences between the donor hearts in PROCEED II that had **observed** cross-clamp times $\geq$ 4 hours compared to the donor hearts in the Heart EXPAND trial that had **expected** cross clamp times $\geq$ 4 hours.
4. **Differences in Practices for Cardioplegia and Myocardial Protection Protocols for Pre & Post-OCS Heart Perfusion:** PROCEED II was the first pivotal trial conducted of the OCS Heart System and at the time that the protocol was designed and approved by the FDA, TransMedics and the trial investigators did not fully appreciate the importance of standardizing and controlling various aspects of the clinical use model, including cardioplegia and myocardial protection following OCS Heart perfusion. These aspects of the clinical use model were standardized across all investigational sites in the OCS Heart EXPAND trial.

5. **Differences in OCS Device Design:** Following completion of PROCEED II, two major device modifications were made to standardize practices and increase the ease of use of the OCS Heart System, which were implemented in the Heart EXPAND trial. One of these device modifications was the replacement of the infusion pump used for solution administration from an off-the-shelf model (Alaris) to a fully integrated console subsystem (i.e., the Ex-Vivo Solution Delivery Subsystem (SDS)) that led to more consistent adherence with the use model. The second modification was a change in the oxygenator from the Novalung oxygenator (PN 100001800) to the Maquet Quadrox-i oxygenator (PN 100004194) to allow the user to follow a mechanical cooling procedure of the OCS-preserved heart for improved myocardial protection post-OCS. Both of these changes were approved by FDA.

For these reasons, it is appropriate to consider the PROCEED II results independently from the results for Heart EXPAND trial. The PROCEED II trial is supportive evidence and should not be considered as a primary data set when evaluating the OCS Heart System for the EXPAND indication.

2.7. Overall Summary of Clinical Data to Support Initiation of Heart EXPAND CAP

In summary, there have been two US IDE trials and numerous published OUS studies of the OCS Heart System. The existing clinical data support the initiation of this CAP. Specifically:

In summary, there have been two U.S. IDE trials and numerous published OUS studies of the OCS Heart System. The existing clinical data support the initiation of this CAP. Specifically:

- The OCS Heart EXPAND trial: This is the most clinically relevant data to support the CAP given that the donor hearts used were non-standard donor hearts that would mostly go unutilized for transplantation and have the identical eligibility critera proposed in this CAP. OCS Heart EXPAND Trial is 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. Although the data for the Heart EXPAND trial are still being collected, monitored and adjudicated, the preliminary results are very encouraging, demonstrating:
  - Utilization rate of 80.6% of donor hearts that are seldom used for transplantation today. These donor hearts were refused by other, non-EXPAND trial centers an average of 65.6 times but were able to be preserved and 80.6% were successfully transplanted in this study.
  - The incidence of ISHLT severe PGD was 10.7%, and the incidence of ISHLT moderate or severe PGD was 12.0%. These rates compare favorably with or are lower than contemporary literature reporting PGD rates post-heart transplantation from standard criteria donor hearts and based on ISHLT PGD criteria.
  - Survival at 30 days and 6 months was 94.7% and 88%, respectively, with 12-month follow-up still on-going. The deaths have been reviewed and adjudicated by the medical monitor. Four of the deaths are heart graft related with the remainder due to pre-existing conditions or other causes.
- PROCEED II Trial was the first pivotal study of the OCS Heart System. This trial was designed in 2006 and it studied categorically different donor hearts and recipient profiles compared to OCS Heart EXPAND trial. Specifically, PROCEED II studied routine standard

donor hearts that were being used for transplantation at the time. The PROCEED II trial was a randomized study of the OCS Heart System compared to standard of care cold storage, and it enrolled routine standard criteria donor hearts that were transplanted into comparatively lower risk heart transplant recipients. 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).

- Real life clinical experience of the OCS Heart System for preservation of standard criteria donor hearts conducted outside the U.S. at hospitals in Germany and the United Kingdom showed improved rates of survival and lower rates of PGD for OCS compared to standard of care cold storage.
- Real life clinical experience of extended criteria donors, including numerous heart transplants from DCD donors, have been conducted outside the U.S. and the results for utilization and patient survival are very encouraging.

In conclusion, this application includes a substantial body of evidence to support the safety and effectiveness of the OCS Heart System. In particular, the Heart EXPAND trial 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 proposed CAP.

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 8 below.

Figure 8: 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

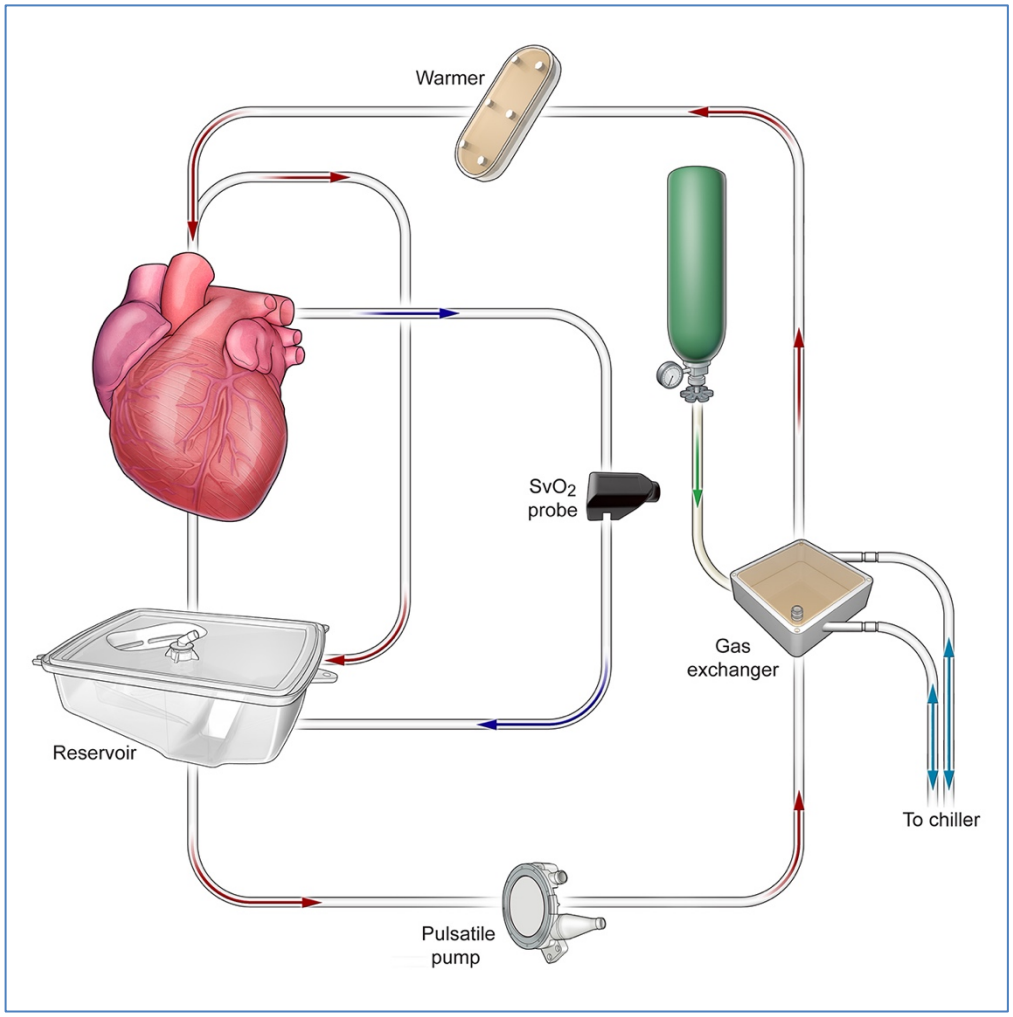
The OCS Heart Solution Set consists of two proprietary heart preservation solutions, a Priming Solution and a Maintenance Solution, to replenish the nutrients and hormones (adenosine) that the metabolically active donor heart requires. The solutions are packaged in a three-chamber bag (nominal volume 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 9 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 9: Schematic of the OCS Heart System Fluid Flow



4. TRIAL OBJECTIVES

The objective of Heart EXPAND CAP is to provide additional data evaluating the safety and effectiveness of the OCS Heart System to preserve and assess donor hearts that do not meet current standard donor heart acceptance criteria for transplantation to potentially improve donor heart utilization for transplantation at a range of transplant centers in the U.S. and to permit patients and physicians access to the OCS Heart System while a PMA application is under preparation and review.

The donor hearts to be evaluated in this trial do not meet current standard donor heart acceptance criteria for one or more of the following reasons:

- Expected total cross-clamp time of ≥ 4 hours
- Expected total cross-clamp time of ≥ 2 hours **PLUS** one or more of the following risk factors:
  - Donor age 45-55 years inclusive, with no coronary catheterization data; or
  - Donor age ≥55 years; or

- Left ventricular septal or posterior wall thickness of >12 mm, but ≤16 mm; or
- Reported down time of ≥ 20 min, with stable hemodynamics at time of final assessment; or
- Left heart ejection fraction (EF) ≥40%, but ≤50% at time of acceptance of offer; or
- Donor angiogram with luminal irregularities with no significant CAD (≤50%); or
- History of carbon monoxide poisoning with good cardiac function at time of donor assessment; or
- Social history of alcoholism with good cardiac function at time of donor assessment; or
- History of diabetes without significant CAD (≤50%) on angiogram.

4.1. Type of Trial

The Heart EXPAND CAP is a prospective, single-arm continuation protocol. The CAP seeks to provide additional data on the safety and effectiveness of the OCS™ Heart System for donor hearts that today may not be transplanted due to the limitations associated with cold storage technique due to the impact of ischemia injury. The CAP permits patients and physicians access to the OCS Heart System while a PMA application is under preparation and review.

4.2. Trial Size and Subject Follow-up

This trial will be conducted at up to 8 institutions, in the United States and will include 75 transplanted heart recipients. The number of subjects was determined based on the enrollment rate for Heart EXPAND and following FDA guidelines for CAPs.

Subjects will be followed for 12 months from the date of transplantation (some of which will be post-market). The summary of follow-up assessments are is summarized in Appendix 2:

- All subjects will be followed from transplant to discharge.
- Patient and graft survival will be documented at Day-30 post transplant.
- Subjects will be followed at 6 and 12 months post-transplant as summarized in Appendix 2.

5. TRIAL ENDPOINTS

5.1. Primary Endpoint

A composite of patient survival at Day 30 and absence of severe primary heart graft dysfunction (PGD) (LV or RV) in the first 24 hours post-transplantation according to ISHLT consensus manuscript (as defined in Appendix 1).

5.2. Secondary Endpoints

- Patient survival and graft survival at Day-30 post transplantation

- Incidence of severe primary heart graft dysfunction (PGD) (LV or RV) in the first 24 hours post-transplantation according to ISHLT consensus manuscript (as defined in Appendix 1)
- Rate of donor heart utilization, defined as the proportion of eligible donor hearts that were successfully transplanted after preservation and assessment 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, defined as:

- Moderate or Severe primary heart graft dysfunction (PGD) (left or right ventricle) (not including rejection or cardiac tamponade) according to ISHLT consensus manuscript.
- Primary graft failure requiring re-transplantation.

5.4. Other Endpoints

- Patient survival at 6 and 12 months post-transplant
- Incidence of primary graft failure requiring re-transplantation through 12 months post-transplant
- Duration of initial post-transplant ICU stay
- Duration of initial post-transplant hospital stay.

6. TRIAL POPULATION

The trial will consist of 75 heart transplant recipients, aged ≥18 years, at up to 8 investigational sites in the US.

6.1. Donor Eligibility Criteria

Donor Inclusion Criteria

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

- Expected total cross-clamp time of ≥4 hours; or
- Expected total cross-clamp time of ≥2 hours **PLUS** one of the following risk factors:
  - Donor age 45-55 years, inclusive, with no coronary catheterization data; or
  - Donor age ≥55 years; or
  - Left ventricular septal or posterior wall thickness of >12 mm, but ≤16 mm; or
  - Reported down time of ≥20 min, with stable hemodynamics at time of final assessment; or
  - Left heart ejection fraction (EF) ≥40%, but ≤50% at time of acceptance of offer; or
  - Donor angiogram with luminal irregularities with no significant CAD (≤50%); or

- History of carbon monoxide poisoning with good cardiac function at time of donor assessment; or
- Social history of alcoholism with good cardiac function at time of donor assessment; or
- History of diabetes without significant CAD on angiogram (≤50%).

Donor Exclusion Criteria

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

- CAD with >50% stenosis on angiogram, or
- Cardiogenic shock or myocardial infarction, or
- EF consistently <40%, or
- Significant valve disease except for competent bicuspid aortic valve.

6.2. Recipient Eligibility Criteria

Recipient Inclusion Criteria

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

- Registered primary heart transplant candidate
- Age ≥18 years old
- Written informed consent.

Recipient Exclusion Criteria

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

- Prior solid organ or bone marrow transplant
- Chronic use of hemodialysis or renal replacement therapy for diagnosis of chronic renal insufficiency requiring dialysis
- Multi-organ transplant.

6.3. Subject Enrollment and Screen Failures

As part of the screening process, the following must occur:

- Subject must be matched with a donor heart that meets eligibility criteria for Heart EXPAND CAP; and
- Subject must meet eligibility criteria for Heart EXPAND CAP; and
- The matched donor heart must be accepted for transplantation in the donor chest by the transplant surgeon or designee; and
- The matched donor heart must be instrumented on the OCS.

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

- The donor heart matched to this recipient fails to meet transplantability criteria per Section 7.4 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 donor heart is instrumented on the OCS™ Heart System and accepted for transplantation following OCS instrumentation preservation.
- Logistical reasons prevent transplantation of 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 when the subject is transplanted with the OCS-instrumented organ.

Subjects who are screen failures that remain eligible for the study will return to the waiting list for another heart transplant. Depending on the donor match, this next transplant may be either in the Heart EXPAND CAP or the subject may be transplanted using standard cold storage and will not be enrolled in this study.

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.

7. PRE-OPERATIVE TRIAL PROCEDURES

7.1. Subject Identification

All patients on the transplant waiting list, or in the process of listing on the transplant waiting list, who are approached by trial investigators for consent for this trial will be identified in a “screening log.”

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 for participation in the trial prior to treatment. When a matching eligible donor heart becomes available, the inclusion and exclusion criteria for the recipient will be re-verified.

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. The following information will be verified on the day of transplant:

- **Eligibility:** Investigator will review and confirm that the potential recipient is still a candidate for heart transplantation and continues to meet all inclusion criteria and no exclusion criteria for this study.
- **Demographics/Characteristics**
- **Recipient Risk Factors & Medical History**

7.3. Donor Screening and Acceptance

The investigator or a member of her/his transplant team will evaluate the donor and the quality and suitability of the heart for: (1) transplantation, according to his or her standard practice and (2) eligibility for the Heart EXPAND CAP. The following evaluations will be conducted:

- **Organ Donor Identification Number and Type of Registry (e.g., UNOS ID)**
- **Donor Demographics**
- **Donor Characteristics**
- **Donor's Cause of Death**
- **Donor Medical History**
- **Donor Social History**
- **Donor Heart Assessment:** An EF is required to determine subject eligibility. The donor heart can be assessed prior to procurement and acceptance using one or more of the following methods:
  - Angiogram findings (if available)
  - Echocardiogram findings (if available)
  - Final inspection and palpation prior to acceptance in the chest
- **Donor Eligibility:** The donor will be evaluated to document whether the eligibility criteria for Heart EXPAND CAP are met.

7.4. Donor Heart Retrieval and OCS Preservation and Assessment

After final evaluation of the donor heart in the donor's chest and after a decision is made to procure the organ for transplantation, donor eligibility for Heart EXPAND CAP will be reviewed. Upon acceptance into the trial, the investigators will retrieve and preserve the donor heart according to the OCS Heart Instructions for use (IFU).

7.4.1. Donor Heart Acceptance 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). Parameters should be maintained within the following ranges for acceptance:

- Final arterial perfusate lactate < 5 mmol/L with stable lactate trend
- Stability of OCS Heart Perfusion parameter trends over time within the guidance ranges below:
  - Aortic Pressure (mean AOP): 40-100 mmHg
  - Coronary Flow (CF): 400-900 mL/min.

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

7.4.2. Reject for Transplantation

Donor hearts preserved on the OCS will be rejected for any of the following:

- Transplanting surgeon and/or designee is clinically unsatisfied with donor heart condition/performance on the OCS Heart System at final evaluation, e.g., unstable and rising arterial lactate despite multiple maneuvers to optimize perfusion parameters (increasing AOP and/or CF)
- Final arterial perfusate lactate ≥ 5 mmol/L.

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

8.1. Transplant Details

The following information concerning the transplant procedure will be collected:

- The organ recipient unique post-transplant patient identifier
- Total cross clamp duration in minutes (from donor cross-clamp application to removal of cross-clamp in the recipient)
- 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 Primary Graft Dysfunction (PGD) Surveillance in the first 24 hours (see Appendix 1)
- Initial use of Mechanical Circulatory Support
- Inotropic Support for first 24 hours: the following inotropic medication doses, if available, will be collected at ICU admission T0 and T24 hours after ICU admission post-heart transplantation:
  - Dopamine – mcg/kg/min
  - Dobutamine – mcg/kg/min
  - Amiodarone – mcg/kg/min
  - Milrinone – mcg/kg/min

  - Epinephrine – mcg/kg/min
  - Norepinephrine – mcg/kg/min
- Echocardiogram results in the first 24 hours
- Right Heart Catheter Data between ICU admission T0 and T24 hours after ICU admission post-heart transplantation (not required; collected only if performed as part of the institution's standard of care):
  - Pulmonary Artery Pressures (PAP)
  - Pulmonary Capillary Wedge Pressure (PCWP)
  - Cardiac index (CI)
  - Right Atrial Pressure (RAP)
  - Initial Post-Transplant ICU Stay
- Initial use of Mechanical Respiratory Support
- Initial Post-Transplant Hospital Stay
- Immunosuppression Medications
- Trans-thoracic echocardiogram prior to Discharge
- Patient and Graft Survival at Day 30 (+5 days), patient and graft survival 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 and 12 months post transplant. Although the follow-up may be done via phone contact; medical records may be needed for additional information.

- **6-Month Follow-Up:** At 6 months post transplant (± 30 days), the patient will be evaluated for:
  - Patient and graft survival
  - Whether the patient was re-hospitalized after initial discharge, and, if so, the primary reason for the hospitalization and the length of stay
  - Information will also be collected on any diagnosis of cardiac dysfunction and, if so, the method of diagnosis and treatment.
- **12-Month Follow-Up: At 12 months (± 30 days) post transplant, the patient will be evaluated for:**
  - Patient and graft survival
  - Any diagnosis of cardiac allograft vasculopathy and, if so, the method of diagnosis (e.g., IVUS, coronary angio).

9. EVALUATION OF ADVERSE EVENTS

Only serious adverse events (SAEs) will be captured in this study.

9.1. Serious Adverse Events (SAEs)

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

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

9.2. Anticipated and Unanticipated Serious Adverse Events

The investigator will assess each serious adverse event for whether it is anticipated or unanticipated using the definitions below.

9.3. Heart Graft Related SAEs

Heart Graft Related SAEs (HGRSAEs) are defined as

- Moderate or Severe primary heart graft dysfunction (PGD) (left or right ventricle) (not including rejection or cardiac tamponade) according to ISHLT consensus manuscript.
- Primary graft failure requiring re-transplantation.

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

9.4. Unanticipated Adverse Device Effect (UADE)

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

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

- Acute rejection

- Atrial and ventricular arrhythmias
- Bleeding (major)
- Hemodynamic instability
- Death
- Fever
- Primary Graft Dysfunction
- Respiratory failure
- Graft failure
- Sepsis
- Renal dysfunction
- Hyperammonaemia
- Malignancy (post-transplant lymphoproliferative disorder (PTLD)
- Multiple organ failure
- Myocardial infarction
- Neurological dysfunction
- Hepatic dysfunction
- Diabetes due to steroid and anti-rejection medications
- Gall stones
- Pancreatitis
- Peptic ulceration
- Gastritis
- Gastro esophageal reflux disease (GERD)
- Aspiration
- Cardiac tamponade
- Pneumo-mediastinum
- Pneumothorax
- Hemothorax
- Pleural bleeding
- Pleural effusion
- Venous thromboembolism (deep venous thrombosis [DVT])
- Pulmonary embolism (PE)

- Sternal wound dehiscence
- Organ deemed not transplantable after retrieval
- Stroke
- Psychosis
- Cerebrovascular accident
- Peripheral vascular clotting or occlusion due insertion of mechanical support
- Limb gangrene due to vascular occlusion due insertion of mechanical support
- Use of mechanical circulatory support
- Coagulopathy
- Hyperacute rejection
- 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.

9.5. Reporting of Adverse Events

All SAE information will only be collected from transplant through day 30. 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.

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.

9.5.1. Relationship of an Adverse Events to OCS™ Heart

The investigator will assess the relationship of the serious adverse event 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.
- **Probably Related:** It is more likely than not that there is a reasonable causal relationship between preservation with the OCS™ Heart the adverse event.
- **Possibly Related:** There is a reasonable relationship with preservation with the OCS™ Heart and the adverse event, but the causal relationship is unclear or lacking.

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

9.5.2. 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.

9.5.3. Pre-Existing Conditions

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

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. Transplanted Recipient Population

The transplanted recipient population will consist of all recipients transplanted with OCS Heart-preserved donor hearts. The analyses of all effectiveness and safety endpoints, except the rate of donor hearts utilization that were successfully transplanted after preservation and assessment on the OCS Heart System, will be based on the transplanted recipient population.

10.2.2. OCS Heart Population

The OCS heart population will consist of all donor hearts that are instrumented on the OCS. The analysis of the rate of donor hearts utilization that were successfully transplanted after preservation and assessment on the OCS Heart System will be based on the OCS heart population.

10.3. Statistical Analysis

10.3.1. Primary Endpoint

The primary endpoint will be summarized using counts and percentages and an exact 95% confidence interval for the true percentage based on the binomial distribution.

10.3.2. Secondary Endpoints

Each secondary effectiveness endpoint will be summarized using counts and percentages and an exact 95% confidence interval for the true percentage based on the binomial distribution. The first two secondary effectiveness endpoints will be analyzed using the transplanted recipient population.

The rate of donor hearts that were successfully transplanted after preservation and assessment on the OCS Heart System (i.e., donor heart utilization), will be analyzed using the OCS heart population.

10.3.3. Other Endpoints

Other endpoints for this trial include:

- Patient survival at 6 and 12 months post-transplant
- Incidence of primary graft failure requiring re-transplantation through 12 months post-transplant
- Duration of initial post-transplant ICU stay
- Duration of initial post-transplant hospital stay

Each endpoint will be summarized using counts and percentages and an exact 95% confidence interval for the true percentage based on the binomial distribution.

10.4. Safety

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

- Moderate or severe primary heart graft dysfunction (PGD) (left or right ventricle) (not including rejection or cardiac tamponade) according to ISHLT consensus manuscript.
- Primary graft failure requiring re-transplantation.

This endpoint will be summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum, maximum, and a 95% confidence interval for the mean based on the t-distribution.

10.4.1. Other Safety Analyses

In addition, the numbers and percentages of subjects experiencing at least one (definitely or probably-related) serious device-related AE, at least one unanticipated SAE, and the number and percentage of deaths will all be tabulated. SAEs will also be tabulated using counts and percentages alone and in regards to the relationship of the SAE to the device, and the severity of the SAE.

10.5. Sample Size Determination

This is a continued access protocol and the sample size was not determined using statistical methods.

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 device such as graft failure, primary graft dysfunction, rejection, infection and other organs/systems complications, graft vessel disease (an expression of chronic rejection), infection, abnormal kidney function, diabetes, high level of cholesterol, high blood pressure, cancer and neurological complications.
- **The Potential 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, only 19.4% 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, 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 device 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 80.6% utilization of these extended criteria donor 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

Written informed consent will be obtained from all subjects before any trial-specific procedures are performed.

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 as 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.

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 is 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.

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

15.2. Pre-Investigational (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 nature 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 review and approval of the clinical investigation before it is initiated and to ensure continuing review of the study by the Institutional Review Board, and to keep the sponsor informed of all Institutional Review Board actions concerning the study

- Has adequate facilities and access to an adequate number of suitable subjects to conduct the investigation.

15.3. Periodic Monitoring Visits

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

- Facilities continue to be adequate and acceptable.
- Informed consent has been obtained.
- The protocol is being properly followed.
- The IRB 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. Trial Completion Visit

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

- Ensure that all 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 submitting a protocol deviation form.

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.

Sites must notify their IRB of protocol deviations in accordance with local IRB requirements.

15.7. Medical Monitor

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

- Review reportable serious adverse events, including PGD, that occur over the course of the trial and the subsequent classification of these serious 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 13 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 13: 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.

15.10. 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.

15.11. 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 Medical Monitor.

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, 2018; Squiers, 2018). If hemodynamic data are not collected, the Medical Monitor 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	Recipient Schedule of Assessments						
	Day of Tx	T0*	T24	Discharge	Day 30	Mo 6	Mo 12
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**	X**				
Mechanical Circulatory Support		X	X				
Patient & Graft Survival		X	X	X	X	X	X
Echocardiogram			X	X			
Initial ICU Stay				X			
Initial Hospital Stay				X			
HGRSAEs and SAEs	X	X	X	X	X		
Cardiac Allograft Vasculopathy							X**

*T0 is defined as the time of initial admission to ICU immediately post-heart transplant procedure within a 2 hour window.

**ONLY Tests regularly scheduled per center standard of care or performed due to a clinical cause at these time-points will be collected.

APPENDIX 3. DRAFT PATIENT INFORMED CONSENT FORM TEMPLATE

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APPENDIX 4. DRAFT ELECTRONIC CASE REPORT FORMS

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