INVESTIGATIONAL PLAN/PROTOCOL

International Trial to Evaluate the Safety and Effectiveness of the Portable Organ Care System (OCS™) Lung System for Recruiting, Preserving and Assessing Non-Ideal Donor Lungs for Transplantation (EXPAND II Trial)

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LIST OF ABBREVIATIONS

Term	Definition
ABG	Arterial Blood Gas
AE	Adverse Event
BAL	Bronchoalveolar lavage
BOS	Bronchiolitis Obliterans Syndrome
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft
CF	Cystic Fibrosis
CFR	Code of Federal Regulation
CMV	Cytomegalovirus
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CV	Curriculum Vitae
DCD	Donation after Cardiac Death
DSMB	Data Safety Monitoring Board
DVT	Deep Venous Thrombosis
ECMO	Extracorporeal Membrane Oxygenation
EVLP	Ex-Vivo Lung Perfusion
FDA	Food and Drug Administration
FEV, FEV1	Forced Expiratory Volume, Forced Expiratory Volume in 1 sec.
FEV1/FVC	Forced Expired Volume in 1 second over Forced Vital Capacity
FiO_2	Fraction of inspired oxygen
FVC	Forced Vital Capacity
GFR	Glomerular Filtration Rate
HCO_3	Bicarbonate
HIV	Human Immunodeficiency Virus
ICU	Intensive Care Unit
IFU	Instructions for Use
ISHLT	International Society for Heart and Lung Transplantation
ISO	International Standards Organization
ITT	Intent-to-Treat
LAS	Lung Allocation Score
MedDRA	Medical Dictionary for Regulatory Activities
OCS	Organ Care System
OR	Operating Room
$PaCO_2$	Partial pressure of CO2 in arterial blood
PaO_2	Partial pressure of O2 in arterial blood
PAP	Pulmonary Artery Pressure
PA	Pulmonary Artery
PAWP	Peak Airway Pressure
PCO_2	Pulmonary Carbon Dioxide Pressure
PCWP	Pulmonary Capillary Wedge Pressure
PE	Pulmonary Embolism
PEEP	Positive End Expiratory Pressure

Term	Definition
PGD	Primary Graft Dysfunction
pH	Hydrogen Ion Concentration
PP	Per Protocol
PPH	Primary Pulmonary Hypertension
PRA	Panel reactive antibody
pRBC	Packed Red Blood Cells
PTLD	Post-Transplant Lymphoproliferative Disorder
PVR	Pulmonary Vascular Resistance
Rh	Rhesus Factor in Blood
RR	Respiratory Rate
SAE	Serious Adverse Event
SaO_2	Arterial Oxygen Saturation
SO_2	Oxygen Saturation
SvO_2	Venous Oxygen Saturation
TIA	Transient Ischemic Attack
T0, T24, T48, T72	Time after transplant (0, 24,48, 72 hours)
TPG	Transpulmonary Gradient (mean PAP-PCWP)
TV	Tidal Volume
UADE	Unanticipated Adverse Device Effect
UNOS	United Network for Organ Sharing
UNOS ID	United Network for Organ Sharing Identification Number
VR	Vascular Resistance

OCS™ LUNG EXPAND II TRIAL SYNOPSIS

Protocol Title	International Trial to Evaluate the Safety and Effectiveness of the Portable Organ Care System (OCS™) Lung System for Recruiting, Preserving and Assessing Non-Ideal Donor Lungs for Transplantation (EXPAND II Trial)
Intended Use	The OCS™ Lung System is to be used to recruit, preserve and assess non-ideal donor lungs that may not meet current standard donor lung acceptance criteria from one or more of the following characteristics: • Donor $PaO_2/FiO_2 \leq 300$ mmHg at the time of the offer; or • Expected cross-clamp time of > 6 hours for the second lung; or • Donor after Cardiac Death (DCD donor); or • Donor age ≥ 55 years old
Objectives	To evaluate the safety and effectiveness of the OCS™ Lung System to recruit, preserve and assess non-ideal donor lungs that may not meet current standard donor lung acceptance criteria (as identified above) for transplantation.
Trial Design	A prospective, pivotal, international single-arm trial referencing the INSPIRE Trial of standard/ideal donor lungs Control Arm and the NOVEL trial of non-ideal donor lungs utilization to benchmark co-primary effectiveness endpoints.
Trial Size	A maximum of 20 participating sites worldwide with 90 transplanted lung recipients
Screening and Treatment	Donor lungs will be screened for trial eligibility. Eligible donor lungs will be recruited, preserved and assessed with the OCS™. After OCS™ recruitment, preservation and assessment, trial donor lungs will be evaluated for acceptability for transplantation using the standard criteria that are employed today to evaluate organ suitability in the donor (i.e., donor PaO_2/FiO_2 ratio and stable OCS™ Lung System perfusion and ventilation parameters). Primary lung transplant candidates will be screened for trial eligibility. Every eligible candidate will be asked to participate. Eligible lung transplant candidates will receive OCS™-treated donor lungs that have been deemed clinically acceptable for transplantation by the treating transplant clinical team.
Donor Lung Eligibility Criteria	**Inclusion** At least one of the following: • Donor $PaO_2/FiO_2 \leq 300$ mmHg at the time of the offer; or • Expected cross-clamp time > 6 hours for the second lung; or • Donor after Cardiac Death (DCD donor); or • Donor age ≥ 55 years old **Exclusion** • Presence of moderate to severe traumatic lung injury with air and/or blood leak • Presence of confirmed active pneumonia or persistent purulent secretions on repeated bronchoscopy evaluation or ET suction • Previous history of active primary lung disease • Multiple transfusions of >10 pRBCs units within 48 hours of lung offer • ABO incompatibility • Tobacco history of >20 pack years at the time of donation • Positive serology of infection with HIV, Hepatitis C or Hepatitis B virus. (Hepatitis B immunization is not an exclusion criterion)
Recipient Eligibility Criteria	**Inclusion (Day of Transplant)** • Male or female primary double lung transplant candidate • Age ≥ 18 years old • Signed: 1) written informed consent document and 2) authorization to use and disclose protected health information

	Exclusion (Day of Transplant) • Prior solid organ or bone marrow transplant • Single lung recipient • Chronic use of hemodialysis or renal replacement therapy for diagnosis of chronic renal dysfunction requiring dialysis • Participant in any other clinical or investigational trials/programs
Donor Lung on OCS™ Transplant Criteria	**Acceptance Criteria for Transplantation after OCS™ Lung Assessment** All donor lungs preserved on OCS™ Lung System must meet at least one of the two following standard clinical criteria for transplantation: a. Final OCS™ Lung System $PaO_2/FiO_2 \geq 300$ mmHg at the end of OCS™ perfusion b. Stability of PAP, PVR, and PAWP defined to be stable or < 20% worsening (i.e., increase) of each of these parameters from beginning to end of OCS™ perfusion **AND** the following criteria must be met in addition to the above • Lungs are clinically acceptable by the center's trial principal investigator based on their clinical judgment. **Reject for Transplantation** • Lungs did not meet acceptance criteria specified above; or • Transplanting surgeon clinically unsatisfied with lung evaluation on OCS™ (If yes, specify reason.)
Co-Primary Effectiveness Endpoints	A co-primary endpoint consisting of: • Patient survival at Day-30 post-transplantation and at initial hospital discharge post-transplantation, whichever occurs later. • Utilization Rate, defined as the number of donated lungs instrumented on OCS™ that meet inclusion/exclusion criteria for the trial and acceptance criteria for transplantation after OCS™ Lung assessment divided by the total eligible donor lungs instrumented on the OCS™ Lung System.
Secondary Endpoints	• Incidence of Primary Graft Dysfunction (PGD) Grade 3 at T72 hours • Incidence of PGD Grade 3 within the initial 72 hours post-transplantation. • Incidence of PGD Grades 2 or 3 at T72 hours • Incidence of PGD Grades 2 or 3 within the initial 72 hours post-transplantation.
Other Endpoints	• Total ischemia and cross-clamp times • Duration of initial post-transplant invasive mechanical ventilation • Length of initial post-transplant ICU stay • Length of initial post-transplant hospital stay • PGD Scores at T0, T24, T48, and T72 hours post-transplantation • Incidence of BOS at 6, 12, 24, and 36 months post-transplantation (including post-market follow-up) • All-cause mortality at 6, 12, 24, and 36 months post-transplantation (including post-market follow-up) • Lung graft-related mortality at 6, 12, 24, and 36 months post-transplantation (including post-market follow-up)
Primary Safety Endpoint	The primary safety endpoint is the number of lung graft-related serious adverse events through the 30-day follow-up or until initial hospital admission (if longer than 30 days) after transplantation per subject, consisting of the following serious adverse events (at most one per type) as described in Appendix 3: • Biopsy proven moderate or severe acute rejection • Respiratory failure requiring prolonged intubation or reintubation • Bronchial anastomotic complications • Major pulmonary-related infection
Follow-up	All patients will be followed for up to 3 years post-transplant (including post-market follow-up).

Statistical Methods	**Analysis Populations** The transplanted recipient population will consist of all recipients who are transplanted. The Per-Protocol (PP) population will consist of all recipients who are transplanted without a major protocol violation. The primary analyses of all effectiveness and safety endpoints will be based on the Per Protocol population. Supportive analyses for all endpoints will be provided for the transplanted recipient population **Effectiveness** There are two co-primary hypotheses for this trial. • Co-Primary Hypothesis #1 The first co-primary hypothesis is that the proportion of transplanted recipients of lungs preserved using the OCS™ Lung System surviving at Day 30 and at initial hospital discharge post-transplantation (whichever occurs later) is greater than a performance goal based on the corresponding proportion of patients in the Per-Protocol population of the Control arm of the INSPIRE trial (0.939) with a margin of 0.12 (12%). The formal statistical hypothesis test is as follows: H_0: $\pi_{OCS\ Lung} \leq 0.819$ H_1: $\pi_{OCS\ Lung} > 0.819$ where $\pi_{OCS\ Lung}$ is the proportion of transplanted recipients alive Day 30 and at initial hospital discharge. This co-primary effectiveness endpoint will be summarized using a count and percentage with an exact 95% confidence interval for the percentage based on the binomial distribution. A one-sided exact binomial test at the 0.025 significance level will be performed to test the null hypothesis H_0. • Co-Primary Hypothesis #2 The second co-primary hypothesis is that the Utilization Rate (defined above) is greater than a performance goal of 0.54 (54%), which is based on the utilization rate reported for XVIVO in the NOVEL Trial (FDA Executive Summary for XVIVO, p.53). The formal statistical hypothesis test is as follows: H_0: $\pi_{OCS\ Lung} \leq 0.54$ H_1: $\pi_{OCS\ Lung} > 0.54$ where πOCS Lung is the observed utilization rate in the EXPAND trial. This co-primary effectiveness endpoint will be summarized using a count and percentage with an exact 95% confidence interval for the true percentage based on the binomial distribution. A one-sided exact binomial test at the 0.025 significance level will be performed to test the null hypothesis, H_0. **Secondary Effectiveness Endpoints** The secondary effectiveness endpoints will be summarized using counts and percentages and an exact 95% confidence interval for the true percentage based on the binomial distribution. **Safety** Safety will be analyzed principally by examination of the frequency of adverse events. In particular, the number of lung graft-related serious adverse events (SAEs) up to the 30-day follow-up or until initial hospital admission (if longer than 30 days) 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 (as defined in Appendix 3): • Acute rejection

	• Respiratory failure • Bronchial anastomotic complication • Major pulmonary-related infection The primary safety hypothesis is that the mean number of lung graft-related SAEs up to the 30-day follow-up or until initial hospital admission (if longer than 30 days) after transplantation is less than a performance goal based on the corresponding mean in the Per-Protocol population of the Control arm of the INSPIRE trial (0.29 events per subject) with a margin of 0.7 events. Specifically: H_0: $\mu_{OCS\ Lung} \geq 0.99$ H_1: $\mu_{OCS\ Lung} < 0.99$ where $\mu_{OCS\ Lung}$ is the mean number of lung graft-related SAEs through 30 days post-transplantation among transplanted recipients. 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. A one-sided one-sample t-test at the 0.025 significance level will be performed to test the null hypothesis H_0. In addition to the primary safety endpoint, all adverse events will be summarized using standard descriptive statistics.
Determination of Sample Size	The sample size for this trial was determined based on providing adequate statistical power for hypothesis testing of the two co-primary effectiveness endpoints. All sample size calculations were performed using PROC POWER in SAS. For the first co-primary endpoint, the calculations assumed a one-sided exact binomial test, an alpha level of 0.025, a control-based rate of 0.939 with a margin of 0.12 (to derive the performance goal of 0.819), a true survival rate for OCS™ of 0.939, and desired power of 90%. Based on these specifications, the required sample size was determined to be 84 transplanted recipients. For the second co-primary endpoint, the calculations assumed a one-sided exact binomial test, an alpha level of 0.025, a performance goal of 0.54, a utilization rate of 72% for OCS™, and desired 90% power. Based on these specifications, the required sample size was determined to be 84 transplanted recipients. In order to ensure that a sufficient number of subjects are evaluable in the per-protocol population of the trial, 90 transplanted recipients in the study is expected to provide adequate power to evaluate the two co-primary effectiveness objectives given the assumptions described. Due to multiple primary endpoints, the Hochberg Method will be used to control familywise error. The p-values for each of the co-primary endpoints will be ordered from highest to lowest. If the highest p-value is less than 0.025 then both endpoints achieve statistical significance and the null hypothesis of each co-primary endpoint can be rejected. If not, then the lower of the two p-values will be assessed against a significance level of 0.0125. If the adjusted significance level of 0.0125 is applied to any of the co-primary endpoints, the power of that analysis will be greater than 85%. Therefore, the study will be considered successful in either of the two scenarios described above. With regard to the primary safety endpoint, the pre-specified safety margin of 0.7 events per patient, the estimated mean of 0.29 events per patient (with an estimated standard deviation of 2.0), a one-sided alpha of 0.025, and the sample size of 90 transplanted recipients results in power greater than 90% when considering a one-sample t-test on the mean.
Trial Sponsor	TransMedics, Inc. 200 Minuteman Road, Suite 302 Andover, MA, USA 01810

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Lung Transplantation and Current Clinical Challenges

Over the last decade, lung transplantation has evolved as the treatment of choice for a variety of end-stage, terminal lung diseases, such as pulmonary fibrosis, cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD), and primary pulmonary hypertension (PPH). While the demand for lung transplantation globally has increased significantly each year, the utilization or recovery of available donor lungs for transplantation has been limited to approximately 20% of the annual available pool of donor lungs in the U.S. Based on the Organ Procurement and Transplantation Network (OPTN) 2010 report, approximately 10,000 consented, donor lungs annually in the U.S. are not transplanted, depriving thousands of patients the gift of new lungs to treat their end-stage lung disease. The main cause for these unfortunate circumstances is that the current technique for lung preservation using cold flush and storage has the following severe limitations:

- It subjects the donor lungs to significant time-dependent ischemic injuries and subsequent reperfusion injuries that impair lung function post-transplant. This causes transplanting physicians to only select for procurement those lungs most likely to withstand the potential damage associated with cold storage preservation. It also imposes significant time and geographical limitations on the lung retrieval process, adversely impacting the utilization of available donor lungs. In addition, this time-dependent ischemic injury has been directly correlated to post- transplant complications.
- It lacks any perfusion and ventilation capabilities to maintain the lung in a near-physiologic *(in- vivo-like)* environment after the donor lung is retrieved from the body of the donor. This limitation results in significant underutilization of the donor lung pool given that many donor lungs are subject to the negative impact of brain death and other untoward physiological conditions in the body of the donor, prior to their procurement.
- It lacks any ability to evaluate organ function after procurement and preservation to determine the suitability of the donor lungs for transplantation. This significantly limits the utilization of donor lungs that are subjected negative, non-physiologic conditions of brain death in the donor.

1.2. Unutilized Donor Lungs

Below is the published table from OPTN on the annual number of unutilized or non-recovered donor lungs in the U.S., and the clinical reasons for non-recovery. In 2009, there were 10,834 consented, donor lungs that were not utilized in the U.S.; the same year only 1,660 patients underwent lung transplantation.[1] As shown in Table 1 below, the vast majority of reasons for not utilizing the donor lungs result from the existing limitations of cold storage.

Donor lung function is measured as the ratio of partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2 ratio). Poor organ function (defined as a PaO_2/FiO_2 ratio < 300 mmHg) is the primary reason why consented donor lungs are not utilized. Poor organ function often is a result of the non-physiologic conditions that occur in the body of the donor following brain death

and subsequent mechanical ventilation dependency, rather than a physiological impairment of the organ. The ability to remove these donor organs from these harsh conditions in the donor and to preserve them in a healthy *in-vivo-like* environment has been shown to improve donor lung function ex-vivo. Such preservation is not possible with cold, ischemic storage.

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

Table 1: Reasons for Non-Recovery of Consented Organs, 2000 to 2009

Reason for Non-Recovery of Consented Organs	Year									
	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Total	8,113	8,137	8,236	8,520	9,325	9,776	10,683	10,741	10,839	10,834
Cardiac Arrest	52	42	45	34	27	23	45	77	92	47
Organ Unsatisfactory (1)	316	398	431	395	437	545	600	594	618	734
Poor Organ Function	5,808	5,687	5,637	5,662	5,874	6,225	6,327	6,461	6,572	6,508
Donor Medical/Social History	545	506	496	751	808	700	989	874	702	901
Biopsy Findings	3	4	19	6	10	6	11	3	6	6
Positive Hepatitis/HIV/HTLV-1	235	215	231	294	348	377	492	436	340	346
No Recipient Found (2)	510	587	572	563	728	730	952	967	1,240	1,142
Other	646	700	805	815	1,095	1,170	1,267	1,329	1,269	1,150
Total (%)	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Cardiac Arrest	0.6%	0.5%	0.5%	0.4%	0.3%	0.2%	0.4%	0.7%	0.8%	0.4%
Organ Unsatisfactory (1)	3.9%	4.9%	5.2%	4.6%	4.7%	5.6%	5.6%	5.5%	5.7%	6.8%
Poor Organ Function	71.6%	69.9%	68.4%	66.5%	63.0%	63.7%	59.2%	60.2%	60.6%	60.1%
Donor Medical/Social History	6.7%	6.2%	6.0%	8.8%	8.7%	7.2%	9.3%	8.1%	6.5%	8.3%
Biopsy Findings	0.0%	0.0%	0.2%	0.1%	0.1%	0.1%	0.1%	0.0%	0.1%	0.1%
Positive Hepatitis/HIV/HTLV-1	2.9%	2.6%	2.8%	3.5%	3.7%	3.9%	4.6%	4.1%	3.1%	3.2%
No Recipient Found (2)	6.3%	7.2%	6.9%	6.6%	7.8%	7.5%	8.9%	9.0%	11.4%	10.5%
Other	8.0%	8.6%	9.8%	9.6%	11.7%	12.0%	11.9%	12.4%	11.7%	10.6%

Source: OPTN/SRTR Data as of October 1, 2010.
(%) = Percentages are based on totals including missing and unknown.
(-) = None in category.
(1) = Organ Unsatisfactory: Organ Damage or Anatomic Abnormalities.
(2) = No Recipient Found: Recipient Not Located or List Exhausted.
Reasons for non-recovery are shown for all organs from deceased donors who donated at least one solid organ.

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

Over the past 6+ years, there has been a global focus on *ex-vivo* lung perfusion (EVLP) in a near physiologic and ventilated state as a promising technique to overcome the current challenges in lung preservation to increase utilization of donor lungs that are currently not used due to shortcomings of cold storage. Numerous published reports support the clinical approach *of ex-vivo* lung perfusion (EVLP) and its potential advantages.

Currently, there are two clinical approaches focusing on achieving the above goals and maximizing the clinical impact of ex-vivo lung perfusion to address the clinical challenges in lung transplantation:

- There is a non-portable approach in which the donor lungs are first preserved and transported using cold storage, and then recruited and evaluated in a non-portable set-up of perfusion and ventilation standalone devices. This approach is limited in its

capabilities and, more importantly, continues to subject the donor lung to significant cold ischemic injury.

- The portable Organ Care System (OCS™) Lung System that is intended to significantly reduce ischemia and reperfusion injuries to the donor lung; and, enable immediate physiologic preservation, recruitment and standard assessment procedures to evaluate the suitability of the lung for transplantation.

The OCS™ Lung System enables the donor lung to be maintained in a near physiologic functioning state ex-vivo, continuously perfused with a warm oxygenated and nutrient-enriched blood (cellular)-based perfusate. The lung is continuously ventilated using standard ventilation techniques to ensure that lung function can be maintained and measured during preservation and transportation. The OCS™ Lung System may enable the following clinical advantages:

- Reduction of the time-dependent ischemic injury to the donor lungs during preservation, thus eliminating significant logistical and geographical barriers to lung transplantation that currently exist with cold storage preservation.
- Standard ventilator recruitment of the donor lungs ex-vivo, to maximize the chances for successfully utilizing the lungs for transplantation.
- Measuring organ function using standard clinical tests to evaluate gas exchange, perfusion, ventilation and metabolic parameters to allow physicians to judge the suitability of the organ for transplantation using the same criteria that physicians use today when harvesting the organ from the donor, thus substantially minimizing the risk of transplanting poor lungs into recipients.

1.4. Summary of Prior Testing and Investigations

1.4.1. OCS™ Lung System Engineering Testing

The OCS™ Lung System is CE marked and has undergone extensive preclinical testing to demonstrate its safety, effectiveness, and readiness for clinical use. The Lung 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 Lung Perfusion Set will be provided sterile using validated methods, and is appropriately packaged to maintain sterility. The OCS™ has also undergone extensive preclinical bench testing for: electrical safety, electromagnetic compatibility, and validation and verification testing (including validation of the device software). All tests and results have demonstrated that the OCS™ meets its expected performance specifications and is safe and suitable for clinical use.

1.4.2. OCS™ Lung System Pre-Clinical Testing

The OCS™ Lung System was extensively tested using swine lungs for up to 24 hours with excellent clinical results.[4,5,8,25] The OCS™ Lung System has been used in more 30 successful human transplants in Europe for routine donor lungs and donor lungs which do not meet the standard criteria for transplantation.[2,3,8] Initially, the safety and effectiveness of the OCS™ Lung System was investigated in a clinical trial outside the U.S. that enrolled two types of donor lungs: 1) donor lungs that met the standard criteria for transplantation and 2) donor lungs which did not meet the standard criteria for transplantation. In this clinical trial, the OCS™ Lung System was

used to recruit and preserve donor lungs that would not otherwise be accepted for transplantation today due to low PaO_2/FiO_2 ratio, non-heart beating donor and older donors. Donor lungs preserved using OCS™ Lung System were transplanted into 13 patients. There was 100% patient and graft survival at 30 days. In addition, long-term results of these 13 patients were published in The Lancet in Nov. 2011.[21]

1.4.3. OCS™ Lung System Testing - INSPIRE

The INSPIRE trial is a randomized, controlled clinical trial comparing outcomes in patients who receive donor lungs meeting the standard criteria for donation preserved using either OCS™ Lung System or a standard cold preservation solution. The INSPIRE study included 320 subjects at 21 investigational sites in the U.S., Canada, Australia and the European Union and was conducted under IDE [redacted], approved on October 26, 2011. The primary objective of the INSPIRE study was to compare the safety and effectiveness of the OCS™ Lung System with the current cold storage standard of care for the preservation of standard criteria donor lungs. The study was a prospective, multi-center, randomized, controlled investigation with subjects assigned to either the standard cold static organ preservation (control) or to the OCS™ warm, perfused, and ventilated preservation (treatment).

The primary effectiveness endpoint was a composite of patient survival post-transplantation at day 30, and absence of PGD Grade 3 (PGD3) in the first 72 hours post-transplant (T0 – T72 hours). The OCS Arm and OCS Solution subgroup met the primary effectiveness composite endpoint of all cause patient survival at day 30 and absence of ISHLT PGD3 in the first 72 hours post-transplantation. In addition, the OCS Solution subgroup was statistically superior to the Control arm in the PP population ($p=0.035$), for the pre-specified primary effectiveness endpoint. A sensitivity analysis was performed assessing the same composite of the primary effectiveness endpoint with lung graft-related survival at day 30 and absence of ISHLT PGD3 within the first 72 hours. The OCS Arm and OCS Lung Solution subgroup met the non-inferiority test.

The OCS Arm and OCS Lung Solution subgroup successfully met the primary safety endpoint (i.e., the average number of lung graft-related serious adverse events up to the 30-day follow-up after transplantation), demonstrating non-inferiority test as compared to Control Arm ($p<0.0001$). The SAEs and Lung Graft-Related SAEs and AEs observed in the INSPIRE study are those that are expected for lung transplantation and no safety signals were observed. Long-term (12 and 24 month) results provide further support for the safety of the OCS™ Lung System.

In addition, the OCS™ Lung System reduced the incidence of PGD3 in the initial 72-hour period following transplantation, which is one of the most severe complications in lung transplantation and a critical indicator of short-term and long-term patient outcomes. Although the mortality at 30 days was shown to be slightly higher in the OCS™ group primarily due to surgical events, subjects treated with the OCS™ Lung System demonstrated similar mortality in the initial post-transplant hospitalization period and at 12 and 24 months compared to cold storage standard of care.

The OCS™ Lung System has been shown to reduce the incidence of BOS through 24 months after transplant, regardless of whether the patient suffered from PGD3 or not. This provides a substantial clinical benefit because BOS is the most severe complication of lung transplant and is a surrogate for eventual long-term graft failure, leading to re-transplant or death. A reduction in BOS through 24 months demonstrates a clinical benefit that is well accepted by the clinical community and is of great benefit to the patients.

An additional benefit of the OCS™ Lung System is that the ischemic time was significantly shorter for the OCS™ Lung System compared to the Standard of care, despite the fact that the cross-clamp time was significantly longer. This may allow increased flexibility for matching donors and recipients and also permits a more in-depth assessment of the donor organ after harvest but prior to transplantation.

The results of the INSPIRE trial have been presented at the ISHLT, and a manuscript is in preparation.[51, 52, 53]

1.4.4. OCS™ Lung System Testing - EXPAND

The Lung EXPAND I study is a single arm, international study of 79 lung transplant recipients enrolled at 8 sites as of December 7, 2016. This investigational study evaluated the safety and effectiveness of the TransMedics OCS™ Lung System to recruit, preserve, assess, and transport non-ideal donor lungs that do not meet the current standard donor lung acceptance criteria for transplantation into a recipient.

The study is on-going and preliminary results have been presented at the 2016 ISHLT meeting (Loor, et al.).[54] The most recent accepted FDA progress report provides the data on all patients transplanted through April 19, 2016 and followed through 30 days post-transplantation. Sixty-two (62) subjects had been transplanted (42 in the U.S). For fifty-six (56) patients the 30-day post-transplant timepoint has been reached (one patient expired) while six are still within the 30-day window. Seventy-two (72) donor lungs have been retrieved with 62 transplanted and 10 not transplanted. Of the 10 preserved lungs not transplanted, 5 were from DCD donors, 5 from donors with age > 55, 2 with low P/F ratio, and 2 from donors with >6 hours cross clamp time.

Two (2) of the 10 donor lungs were not transplanted due to reasons unrelated to lung condition. In both cases, the lungs performed well on OCS™ and would have been suitable for transplant, but were not used due to issues with the recipient. Therefore, the utilization rate for these non-ideal donor organs is 88.6% (62/70).

Donor lung characteristics are shown Table 2 below. The retrieved donor lungs met several eligibility criteria including donor age > 55 years (43%), expected cross clamp time > 6 hours for the second lung (38%), PaO_2/FiO_2 < 300 mm Hg at final offer (29%) and Donation after Circulatory Death (DCD) (30%).

Table 2: Donor Lung Characteristics in EXPAND I

	OCS Lung Transplants (n=56)
Age (Years): Mean ± SD	48.0 ± 15.7
Donor Eligibility Criteria	
PaO_2/FiO_2 Ratio ≤ 300 mmHg	29%
Expected Cross Clamp Time > 6 hours	38%
DCD Donor	30%
Donor Age >55 yr	43%
≥ 1 Eligibility Criteria (from above list)	34%

There is 98% survival of subjects at 30 days and 95% survival of subjects during the initial hospitalization.

The safety endpoint is the number of LGRSAEs through the 30-day follow-up period after transplantation per subject. Thirteen (13) subjects experienced 14 LGRSAEs within 30 days post-transplant. Eleven (11) were respiratory failure, which includes protracted ventilation and 3 were major pulmonary infections. There were no incidences of bronchial anastomotic complication or acute rejection (biopsy-proven). These rates of LGRSAEs are not unexpected, given the fact that this study focuses on non-ideal donor lungs. Long-term follow-up is continuing.

Table 3: Safety Endpoint Results

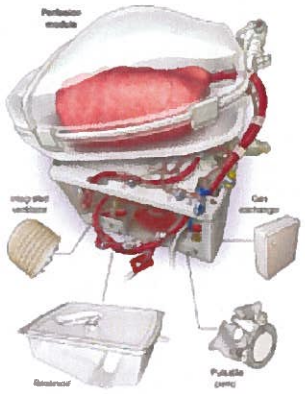
Lung Graft-Related SAEs (LGRSAEs)	Incidence Rate
Subjects with at least one LGRSAE within 30 days	13/56 (23%)
Respiratory failure/Protracted ventilation	11/56 (20%)
Major pulmonary-related infection	3/56 (5%)
Bronchial anastomotic complication	0/56 (0%)
Biopsy-proven acute rejection	0/56 (0%)

2. DEVICE DESCRIPTION

TransMedics developed an integrated, portable ex-vivo perfusion and ventilation system for donor lung preservation for transplantation. The donor lung is maintained in normothermic temperature, perfused with high-oncotic perfusion solution that is supplemented with packed red blood cells (pRBCs) and ventilated with oxygenated gas to enable the lung to be in near-physiologic condition and minimize ischemic injury on the donor lungs intended for transplantation. The OCS™ Lung System is composed of 3 major components:

- **OCS™ Lung Console (Lung Console):** This is a portable electromechanical device that contains a pulsatile pump motor, variable mode ventilation system, universal power system, electronics and wireless monitor.
- **OCS™ Lung Perfusion Set (LPS):** The LPS consists of the Lung Perfusion Module (LPM) and LPS Accessories. The LPM is a biocompatible single use disposable set that contains embedded sensors (e.g., pressure and temperature), perfusion and ventilation circuits and perfusate sampling ports. The LPS Accessories are sterile, disposable accessories necessary to instrument the lung and manage the perfusate.
- **OCS™ Lung Solution:** This is a high oncotic solution used for ex-vivo flush and perfusion of donor lungs when combined with packed red blood cells (pRBCs)

Figure 1: OCS™ Lung System Components

		
OCS™ Lung Console	**OCS™ Lung Perfusion Module (LPM)**	**OCS™ Lung Solution**

3. TRIAL OBJECTIVES

To evaluate the safety and effectiveness of the OCS™ Lung System to recruit, preserve and assess donor lungs that may not meet current standard donor lung acceptance criteria from one or more of the following characteristics:

- Donor $PaO_2/FiO_2 \leq 300$ mmHg at the time of the offer; or
- Expected cross-clamp time of > 6 hours for the second lung; or
- Donor after Cardiac Death (DCD donor); or
- Donor age ≥ 55 years old

3.1. Type of the Trial

A prospective, pivotal, international single-arm trial of donor lungs and donor lung transplant recipients.

The proposed clinical trial seeks to evaluate the safety and effectiveness of the OCS™ Lung System for donor lungs that today may not be transplanted due to the limitations associated with cold storage technique (such as ischemia and the inability to evaluate organ function following preservation and ventilation). The results of the OCS™ Lung System with non-ideal donor lungs in this study will be compared to the results for both the control arm of the INSPIRE trial and to the results of the NOVEL study of the XVIVO EVLP system.

3.2. Size, Subject Follow-up

This trial will be conducted at no more than 20 institutions, in the U.S. and world-wide (Europe, Australia and Canada) and will include up to 90 transplanted lung recipients. The number of subjects was determined as described in the statistical analysis section of this Investigational Plan/Protocol. Subjects will be followed for up to 36 months from the date of transplantation. The details of the follow-up are summarized in Appendix 4 as follows:

- All subjects will be followed from transplant to discharge.
- Patient survival will be documented on Day 30 post-transplant and at initial hospital discharge following transplantation.
- Patient survival and clinical diagnosis of BOS will be documented at 6, 12, 24, and 36 months patient follow-up (these are post-market follow-up timepoints) per Appendix 4.

4. TRIAL ENDPOINTS

4.1. Primary Effectiveness Endpoint

The study will evaluate two co-primary effectiveness endpoints:

- Patient survival at both 30 days and at initial hospital discharge post-transplantation, whichever occurs later. The basis for this endpoint is the control arm of the INSPIRE trial with a 12% margin.
- Utilization Rate, defined as the number of donated lungs instrumented on OCS™ that meet inclusion/exclusion criteria for the trial and acceptance criteria for transplantation after OCS™ Lung assessment divided by the total eligible donor lungs instrumented on the OCS™ Lung System. The basis for this endpoint is the utilization rate reported for XVIVO in the NOVEL Trial.

Survival at initial hospital discharge post-transplantation is considered to be survival during the initial hospital admission for the transplant procedure through the date of discharge if it is longer than 30 days.

4.2. Secondary Effectiveness Endpoints

The study will evaluate the following secondary effectiveness endpoints:

- Incidence of Primary Graft Dysfunction (PGD) Grade 3 at T72 hours
- Incidence of PGD3 within the initial 72 hours post-transplantation
- Incidence of PGD Grades 2 or 3 at T72 hours
- Incidence of PGD Grades 2 or 3 within the initial 72 hours post-transplantation.

4.3. Other Endpoints

- Total ischemia and cross-clamp times
- Duration of initial post-transplant invasive mechanical ventilation
- Length of initial post-transplant ICU stay
- Length of initial post-transplant hospital stay
- PGD Scores at T0, T24, T48, and T72 hours
- Incidence of BOS at 6, 12, 24, and 36 months post-transplantation (including post-market follow-up)

- All-cause mortality at 6, 12, 24, and 36 months post-transplantation (including post-market follow-up)
- Lung graft-related mortality at 6, 12, 24, and 36 months post-transplantation (including post-market follow-up).

4.4. Primary Safety Endpoint

The primary safety endpoint is the number of lung graft-related serious adverse events through the 30-day follow-up or until initial hospital admission (if longer than 30 days) after transplantation per subject. This endpoint is defined to consist of the following serious adverse events (at most one per type):

- Biopsy proven moderate or severe acute rejection
- Respiratory failure requiring prolonged intubation or reintubation
- Bronchial anastomotic complications
- Major pulmonary-related infection.

A more complete description is provided in Appendix 3.

5. TRIAL POPULATION

The trial will include 90 double-lung transplant recipients, at up to 20 investigational sites in the U.S. and world-wide (Europe, Australia and Canada).

5.1. Donor Eligibility Criteria

5.1.1. Donor Inclusion Criteria

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

- A donor PaO_2/FiO_2 ratio of ≤ 300 mmHg at the time of the offer; or
- Expected cross-clamp time of > 6 hours for the second lung; or
- Donor after cardiac death (DCD donor); or
- Donor age ≥ 55 years old.

5.1.2. Donor Exclusion Criteria

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

- Presence of moderate to severe traumatic lung injury with air and/or blood leak
- Presence of confirmed active pneumonia or persistent purulent secretions on bronchoscopy evaluation or ET suction
- History of primary active lung disease
- Multiple transfusions of >10 pRBCs units within 48 hours of lung donor offer
- ABO incompatibility
- Tobacco history of >20 pack years at the time of donation

- Positive serology of infection with HIV, Hepatitis C or Hepatitis B virus. (Hepatitis B immunization is not an exclusion criterion).

5.2. Recipient Eligibility Criteria

5.2.1. Recipient Inclusion Criteria

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

- Male or female primary double-lung transplant candidate
- Age ≥ 18 years old
- Signed: 1) written informed consent document and 2) authorization to use and disclose protected health information.

5.2.2. Recipient Exclusion Criteria

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

- Prior solid organ or bone marrow transplant
- Single lung recipient
- Chronic use of hemodialysis or renal replacement therapy for diagnosis of chronic renal dysfunction
- Participant in any other clinical or investigational trials/programs.

6. PRE-OPERATIVE TRIAL PROCEDURES

6.1. Recipient Day of Transplant Assessment

The purpose is to conduct a final assessment of whether the subject still meets the eligibility criteria. The information below will be verified and recorded on the day of transplant.

- **Eligibility:** Investigator will review and confirm that the recipient continues to meet all inclusion criteria and no exclusion criteria.
- **Demographics/Characteristics:** The recipient's demographics, such as date of birth, (if applicable) gender, race, ethnicity, weight , height and BMI will be obtained. Date of consent, Recipient ID, Lung Allocation Score (LAS), and other recipient characteristics, such as blood type and RH factor, will be collected as well.
- **Recipient Risk Factors & Medical History:**
  - Indication for Transplantation: The etiology of lung failure will be obtained (e.g., Cystic fibrosis, COPD, Idiopathic Pulmonary Fibrosis (IPF), Bronchiectasis, Idiopathic Pulmonary Arterial Hypertension (IPAH), or other (needs to be specified).
  - Circulatory Mechanical Support: Investigator or trial coordinator will document if the recipient is using ECMO on the day of transplant and the reason (for respiratory function support).

- Invasive Ventilator Support: Investigator or trial coordinator will document if the recipient is on invasive ventilator support and the start date.
- Systemic Diseases: Including the presence of right or left-sided heart failure, sarcoidosis, venooclusive disease, or secondary pulmonary hypertension.
- Renal Status: The investigator will confirm that the patient is not on renal replacement therapy including dialysis, hemofiltration, or peritoneal dialysis.

6.2. Donor Screening and Acceptance

Using the inclusion and exclusion criteria, the investigator or a member of her/his transplant team will evaluate the donor and the quality and suitability of the lungs for the trial. The evaluations below will be conducted and recorded only if the donor lung was instrumented on OCS™ for recruitment, preservation and assessment for potential transplantation into a consented recipient.

- Organ Donor Identification Number and Type of Registry (e.g., UNOS ID, Eurotransplant ID)
- **Demographics:** Age, date of birth (if available), gender, ethnicity and/or race of the donor
- **Donor Characteristics:** Blood type,
- **Donor's Cause of Death:** The donor's cause of death will be collected. Any cardiac arrest details will also be recorded including duration and whether it was witnessed or not.
  - For DCD donors, time of withdrawal of support, time of announcement of cardiac death, and total warm ischemic time (time from withdrawal of support until the cross clamp time in the donor chest) will be collected
- **Medical History:** Relevant present medical history, including present history (As of current hospital admission) of pneumonia or chest injury, history of any aspirations. CMV, HIV, Hepatitis B or C, and malignant tumors. In addition, number and volume of blood transfusions will be collected, if applicable.
- **Social History:** Smoking, drugs, and any environmental inhalation injuries
- **Lung Oxygenation Capacity:** Donor arterial blood PaO_2/FiO_2 ratio at time of initial donor offer, ventilation parameters (Tidal Volume, PEEP and FiO_2) as recorded in the donor's offer sheet will be collected and recorded to assess lung function
- **Donor Lung Assessment:** The donor lung will be assessed prior to procurement and acceptance using the following methods:
  - **Chest X-ray OR CT Scan (if available):** Evaluated for any potential pathology (e.g., pulmonary contusions, pulmonary edema, mass, infiltrates, pneumothorax or pneumonia).
  - **Bronchoscopy:** Bronchoscopic examination of airway should be carried out prior to procurement. Any findings/ abnormality at the final bronchoscopic examination (e.g., excessive secretions, ulcers, mucopurulent secretions or bleeding) will be recorded.

- **Final inspection at final physical examination prior to acceptance in the chest:** The donor lung will be evaluated for any contusions, nodules, masses, bullae, atelectasis, pneumonia or any gross abnormalities as documented in the donor run sheet or retrieval surgical note. All final lung evaluations including duration of the donor on mechanical ventilation will be collected

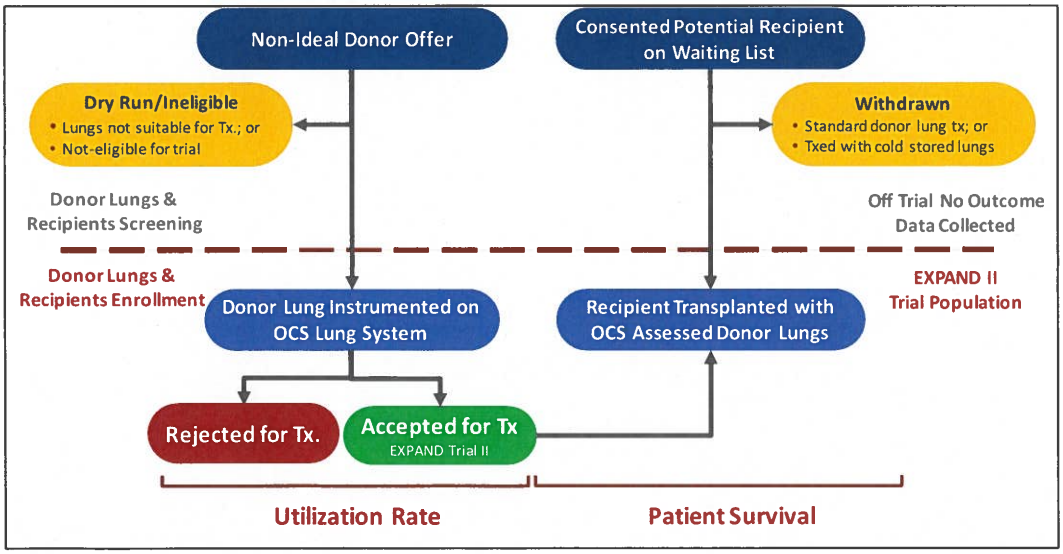
- **Eligibility:** The donor will be evaluated to document whether the eligibility criteria are met. All eligibility criteria or clinical reasons for not accepting a donor lung at final assessment before retrieval will be recorded.

- **Donor Allocation Status:** The donor lung run match status will be collected for donor lungs preserved on OCS™ when applicable. If the donor lungs were rejected by other centers, number of times lungs were rejected, sites names (up to the last 3 centers) and the reasons for lung allocation rejection will be collected when applicable.

6.3. Subject Identification

All patients on the transplant waiting list, or in the process of listing on the transplant waiting list, who are being approached by trial investigators for consent for this trial will be identified in a "screening log" that is maintained by the trial coordinator. Those patients who initially appear eligible for the trial will have the trial thoroughly explained to them, be invited to participate, and will be asked to sign an informed consent for participation in the trial prior to treatment. Only when a final decision is made that donor lungs have met the transplantability criteria on the OCS™ Lung System, the recipient will be assigned a subject identification number. Consented recipients who were transplanted using standard ideal donor lungs outside of the study, or who were transplanted with lungs preserved using cold storage preservation outside of the study, will be considered withdrawn from the EXPAND II Study. Figure 2 below is a flow diagram of donor lung and potential transplant recipients screening and enrollment process for the EXPAND II Trial.

Figure 2: OCS™ Lung EXPAND II Trial Donor Lungs and Recipients Screening and Enrollment Flowchart



A consented potential recipient will be considered withdrawn from the EXPAND II Trial under the following conditions:

- The patient was transplanted using standard donor lungs; or
- The patient was transplanted using cold storage for preservation of the donor lungs.

Potential donor lungs will be considered as a dry run/ineligible under the following conditions:

- The clinical retrieval team deemed the lungs not suitable for clinical transplantation due to pathology or lung conditions;
- Donor lungs did not meet eligibility criteria for the EXPAND II Trial.

To clarify, no clinical outcomes data will be collected on withdrawn recipients or dry run/ineligible donor lungs as defined above.

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

- The recipient fails to meet inclusion/exclusion criteria on the day of the potential transplant when eligible donor lungs are accepted for transplantation after OCS™ Lung System preservation and assessment.
- Transplant center or OPO logistical reasons prevent transplantation of donor lungs preserved using the OCS™ Lung System:
  - Surgeons or Operating Rooms are not available to perform the lung transplant procedure preventing the use of the donor lung for transplantation preserved on the OCS™ Lung System, despite meeting OCS™ Lung transplantation acceptance criteria (Section 6.5 below).
  - Transportation or allocation logistics issues while a donor lung is instrumented on OCS™ Lung System preventing the use of the donor lung for transplantation despite meeting OCS™ Lung transplantation acceptance criteria (Section 6.5 below).

All screen failures and reasons for screen failure will be documented.

6.4. Donor Lung Retrieval and OCS™ Preservation and Assessment

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

- **Initial Lung Flush in Donor Body:** all donor lungs will be flushed using
  - *Antegrade flush* = 3-5 L of cold buffered OCS™ Lung Solution supplemented with 50 mg of nitroglycerin according to the Instructions for Use (IFU)
  - *Retrograde flush = 1-2 L of cold buffered OCS™ Lung Solution*
  - Lung flush will be delivered by gravity (no pressurized bags)

  OCS™ Lung Solution will be buffered before use by adding either one of the following buffering agents:
  - 1 mmol of THAM (Tromethamine®)/ 1L (bag) of solution, OR

- 10 meq. of $NaHCO_3$ per 1L (1 bag) of solution **OCS™ Lung System Perfusion & Ventilation:** The OCS™ Lung System will be primed using 1.5-2 L of buffered OCS™ Lung Solution supplemented with 3 units of allogeneic packed RBCs, aiming to achieve a target hematocrit of 15%-25% on the OCS™ Lung System. The allogeneic packed RBCs must be ABO compatible to the transplant recipient, tested CMV negative, leukocyte-reduced, and meet all other eligibility requirements for allogeneic packed red blood cells. Lungs preserved on the OCS™ Lung System should be maintained according to the OCS™ Lung System IFU for up-to 10 hours.
- **The OCS™ Lung System Preservation Parameters:** The OCS™ device parameters will be maintained within the following ranges
  - TV: 6mL/Kg (Donor's ideal body weight)
  - Respiratory rate: 12 breaths/min
  - PEEP: 5-9 cmH_2O
  - Pump flow: 1.5-2 L/min during preservation and transportation. Pump flow may be adjusted to 2-3L/min during assessment of donor lungs on OCS™ in Continuous Monitoring Mode
- **Final Lung Flush Post-Ex-vivo perfusion on OCS™ Lung System:** Termination of lung preservation on the OCS™ Lung System should be maintained according to the OCS™ Lung IFU. All donor lungs perfused on the OCS™ Lung System will be flushed using 3-5 L of cold buffered OCS™ Lung Solution according to the IFU.

The following information will be collected:

- **Operative Details:** The following information will be collected at time of lung retrieval
  - Donor hospital name, city, state /country (when applicable)
  - Surgical observations relating to donor lung (donor lung tear, adhesions, surgical injury, contusion, or bullae)
  - Date and time of cross clamp of donor pulmonary artery (PA)
  - For DCD donors, dates and times will be collected for the following:
    - Withdrawal of support
    - Announcement of cardiac arrest
    - Cross clamp of the Pulmonary Artery
  - 1st and 2nd transplanted lung cross-clamp times
  - 1st and 2nd transplanted lung ischemic times
  - Use of Cardiopulmonary Bypass CPB (if applicable) and length of time on CPB will be collected.
- **OCS™ Details** (lung instrumentation details):
  - Donor lungs instrumentation on the OCS™ Lung System date and time
  - Perfusate volume and ABO type of the pRBCs units used to prime the OCS™.

- **OCS™ Measurements:** The following OCS™ Lung System perfusion and ventilation parameters as well as lung oxygenation capacity will be recorded:
  - Final PaO_2/FiO_2 ratio on OCS™ (at initial and final Continuous Monitoring Mode at the recipient's hospital after the retrieval)
  - Mean Pulmonary Artery Pressure (PAP) trend
  - Pulmonary Vascular Resistance (PVR) trend
  - Peak Airway Pressure (PAWP) trend.

6.5. Donor Lung Acceptance for Transplantation After OCS™ Lung Assessment

- All donor lungs preserved on OCS™ Lung System must meet at least one of the two following standard clinical criteria for transplantation at final assessment on OCS™ Lung System[11]:
  - Final OCS™ Lung System PaO_2/FiO_2 ratio of ≥300 mmHg at the end of OCS™ perfusion
  - Stability of PAP, PVR, & PAWP trends defined to be stable or <20% worsening (i.e., increase) of each of these parameters from beginning (at initial assessment in Continuous Monitoring Mode) to end of OCS™ perfusion (at final assessment in Continuous Monitoring mode)

AND the following criteria must be met in addition to the above:

- Lungs are clinically acceptable by the Site Principal Investigator based on their clinical judgment.

- Any decision to turn down lungs after the lungs have been retrieved, preserved and assessed on OCS™ Lung System should be done with notification to the Site Principal Investigator and document the clinical reason for turning down the donor lung for transplantation.

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

7.1. Transplant Details

- Information concerning the transplant procedure, such as: name of the surgeon, organ recipient unique post-transplant patient identifier, date of transplant, skin incision time, the use of and duration on cardiopulmonary bypass, time of completion of procedure/ OR discharge time.
- Any procedural related complication will be collected and recorded.
- Any concomitant surgical procedure done at transplantation (e.g., Tricuspid valve annuloplasty, CABG) will be collected and recorded.

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

- **Primary Graft Dysfunction** (PGD) Surveillance at T0, T24, T48, and T72 hours (see Appendix 1):
  - Chest X-ray: Serial chest x-rays will be performed and the reports will be recorded at the above timepoints to guide the diagnosis of PGD at T0, T24, T48, and T72.
  - Arterial Blood Gas Analysis: Arterial blood gas analysis will be performed and the results will be recorded at the above timepoints to guide the diagnosis of PGD at T0, T24, T48, and T72 to evaluate gas exchange function of the lungs. PaO_2/FiO_2 ratio will be calculated to guide the diagnosis of PGD that will be evaluated at T0, T24, T48, and T72.
  - ECMO use and reason as well as status of mechanical ventilation will be collected.
  - For Extubated patients at time of assessment of PGD, supplemental oxygen therapy method of delivery (e.g., nasal cannula, face mask), FiO_2, volume of supplemental oxyegen (L/min) and the use of nitric oxide use (if applicable) will be collected and recorded.
- **Initial Use of Mechanical Respiratory Support:** Type and duration of invasive ventilator support post-transplant with ventilation settings for oxygenation post-transplant will be recorded
- **Initial ECMO Use for Oxygenation Support:** If ECMO was used for oxygenation support, it will be recorded. If ECMO was used for pre-specified site specific protocol for a reason other than oxygenation support, the clinical reasons will be recorded.
- **Initial Post-Transplant ICU Stay:** Intensive care unit (ICU) admission time, and date and time when clinical order for ICU discharge is written, and date and time of actual ICU discharge will be recorded. Any ICU readmissions will be recorded. If the patient's ICU stay is prolonged, due to complications not related to the graft function or due to logistical issues, this information will also be captured.
- **Standard of Care Pulmonary Function Tests :** Will be collected (within 90 days post lung transplant depending on patient's condition). If not done, reason should be specified and recorded
- **Standard of Care Bronchoscopy & Trans-bronchial Biopsy/Bronchoalveolar Lavage Prior to Discharge (if applicable):** A fiber optic bronchoscopy evaluation may be conducted and recorded prior to initial hospital discharge to assess airway healing and to obtain biopsy samples. A lung biopsy and bronchoalveolar lavage samples may be collected for subsequent evaluation at the investigational sites for acute rejection episodes and infection. If performed, the ISHLT revised rejection grading system will be utilized to evaluate any diagnosed rejection episode according to (see Appendix 2).

- **Patient and Graft Survival at Day 30 and at Initial Hospital Discharge if Greater than 30 Days:** Patient and graft survival will be assessed and recorded on day 30 post-transplant and at initial hospital discharge if greater than 30 days.
- **Adverse Events:** All serious adverse events and any new lung graft-related adverse events will be followed and documented until the investigator designates the event to be either resolved or its effect on the patient's condition stabilized.
- **Medications:** Medications used to treat all serious adverse event (SAE)-related will be recorded in the trial database until the SAE is resolved.

These follow-ups will be attempted within +2 days of the designated periods except for the PGD scores at T0, T24, T48, and T72 which must be collected on the designated days. The evaluations may be conducted over several days.

7.3. Long-Term Follow-up: 6, 12, 24, and 36 months (Post-Market Follow-up)

Follow-up data collection will be conducted at approximately 6, 12, 24, and 36 months post-transplant.

- **6, 12, 24, and 36 month Follow Up:** At approximately 6, 12, 24, and 36 months post-transplant, the patient will be evaluated at an office visit if this is the institution's standard of care, and, if not, by phone contact by the site. The patient's medical record will be reviewed to confirm patient's answers. This follow-up will collect the following information on transplanted recipients in the trial:
  - Patient and graft survival
  - Whether the patient was hospitalized after initial discharge, and, if so, the primary reason for the hospitalization and the length of stay; these data will be collected only for the 6-month follow-up timepoint.
  - Clinical diagnosis of BOS and method of diagnosis
  - Results of any standard of care or per-cause pulmonary function tests, bronchoscopies, or biopsies

  The 6, 12, 24, and 36 months follow-up will be collected within +30 days of the designated period and will be recorded.

8. EVALUATION OF ADVERSE EVENTS

8.1. Evaluation of Lung Graft-Related Adverse Events

Lung Graft-Related Adverse Events are those which have any untoward effect on the health or safety of the patient and that are directly related to the transplanted lung graft. Lung graft-related adverse events will be collected from the time a subject is transplanted with a lung preserved on OCS™ Lung System until the completion of the 30-day follow-up or until initial hospital admission (if longer than 30 days), which is the window for assessment of safety endpoint. A lung graft-related adverse event will be followed until resolution or stabilization of the event.

8.2. Serious Adverse Events (SAEs)

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

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

All SAEs will be followed until their resolution.

8.3. Anticipated and Unanticipated Adverse Events

The investigator will assess each adverse event for whether it is anticipated or unanticipated to the lung transplant procedure.

The following adverse events are associated with pulmonary transplant procedures and have been documented within the first 30 days after lung transplant, or until initial hospital admission (if longer than 30 days) and are, therefore, anticipated:

- Acute rejection
- Arrhythmia
- Bleeding (major)
- Hemodynamic instability
- Death
- Fever
- Primary Graft Dysfunction (PGD) (see Appendix 1)
- Respiratory failure
- Graft failure
- Focal or systemic major infection (bacterial, viral, fungal)
- Sepsis
- Emphysema
- Tracheobronchitis/pneumonitis/pneumonia
- Renal dysfunction
- Hyperammonaemia
- Malignancy (post-transplant lymphoproliferative disorder (PTLD)
- Multiple organ failure
- Myocardial infarction
- Neurological dysfunction
- Hepatic dysfunction
- Gall stones
- Pancreatitis
- Peptic ulceration

- Gastritis
- Gastro esophageal reflux disease (GERD)
- Aspiration
- Pneumothorax
- Hemothorax
- Pleural bleeding
- Pleural effusion
- Airway anastomotic complications (focal infection, necrosis/dehiscence, stenosis)
- Venous thromboembolism (deep venous thrombosis [DVT])
- Pulmonary embolism (PE)
- Pulmonary infarction
- Wound dehiscence
- Organ deemed not transplantable after retrieval
- Stroke
- Psychosis

8.4. Unanticipated Adverse Device Effect (UADE)

An UADE means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified 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 (21 CFR 812.3(s)).

8.5. Recording and Reporting of Adverse Event

All lung graft-related adverse events and serious adverse events are to be recorded on the case report forms. The description of the adverse event will include the date of onset, duration, severity, seriousness, the relationship of the event to the trial treatment, anticipated or not, and any treatment required. All SAEs will be followed until their resolution.

For all SAEs, the investigator is required to supply any additional data that may be deemed necessary by the Sponsor. Additionally, SAE and unanticipated adverse device effects (UADEs) should be reported to TransMedics, Inc., preferably within 48 hours of the time the investigator learns of the event, but in no case later than 5 working days. For any particular patient, the independent Medical Monitor if required to protect patient safety may specify a different follow-up period. The Sponsor is responsible for the classification and reporting of lung graft-related adverse events to the appropriate regulatory authorities, and for the on-going safety evaluation of the trial in accordance with ISO 14155 and governing regulatory requirements.

8.6. Relationship of an Adverse Events to OCS™ Lung System

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

- **Definitely Related:** There is a reasonable causal and temporal relationship between preservation with the OCS™ Lung System or with preservation with the standard of care and the adverse event.

- **Probably Related:** It is more likely than not that there is a reasonable causal relationship between preservation with the OCS™ Lung System or with preservation with the standard of care and the adverse event.
- **Possibly Related:** There is a reasonable relationship with preservation with the OCS™ Lung System or with preservation with the standard of care and the adverse event, but the causal relationship is unclear or lacking.
- **Not Likely Related:** There is a temporal relationship with preservation with the OCS™ Lung System or with preservation with the standard of care and the adverse event, but there is not a reasonable causal relationship between the trial device and the event.
- **Unrelated:** There is no relationship between preservation with the OCS™ Lung System or with preservation with the standard of care and the adverse event.

8.7. Severity

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

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

8.8. Pre-Existing Conditions

Pre-existing diseases or conditions will not be reported as adverse events unless there has been a substantial increase in severity or frequency of the problem that cannot be attributed to the expected progression of the disease or condition.

8.9. Clinical and Laboratory Changes

The investigator will review the results of all clinical and laboratory tests as they become available. For each laboratory test result, the investigator will ascertain if this is an abnormal (i.e., clinically significant) change from baseline for that individual subject. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is determined to be clinically significant change from baseline for that subject, this will be considered an adverse event.

9. STATISTICAL METHODS

9.1. General

Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized using frequencies and percentages.

Missing outcomes, although not expected, will be addressed through multiple imputation so that analyses are based on complete data.

9.2. Analysis Populations

9.2.1. Transplanted Recipient Population

The transplanted recipient population will consist of all subjects who are transplanted in the trial. Additional supportive analyses of all effectiveness and safety endpoints will be based on the transplanted recipient population.

9.2.2. Per-Protocol (PP) Population

The Per-Protocol (PP) population will consist of all subjects who are transplanted without a major protocol violation. Major protocol violations would be considered:

- Ineligible for the study according to the recipient inclusion and exclusion criteria
- Ineligible for the study according to the donor organ inclusion and exclusion criteria
- Failure to complete adequate post-transplant assessments to support the primary effectiveness and primary safety endpoints
- Failure to follow the IFU for the OCS™ Lung System
- Failure to meet Donor Lung Acceptance for Transplantation after assessment on the OCS™ Lung System, as outlined in Section 6.5.

The primary analysis of all endpoints will be based on the PP population, which is appropriate given that the comparator rate is derived from the Control arm of the PP population from the INSPIRE trial. Supportive analyses will be conducted using the Transplanted Recipient population.

9.3. Analysis of Effectiveness Endpoints

There are two co-primary hypotheses for this trial.

9.3.1. Co-Primary Effectiveness Endpoint #1

The first co-primary hypothesis is that the proportion of transplanted recipients of lungs preserved using the OCS™ Lung System surviving at Day 30 and at initial hospital discharge post-transplantation (whichever occurs later) is greater than a performance goal based on the corresponding proportion of patients in the Per-Protocol population of the Control arm of the INSPIRE trial (0.939) with a margin of 0.12 (12%).

The determination of the margin (12%) is based on the following:

- The estimate observed in the Control arm of the INSPIRE trial [93.9% (169/180)] serves as the target for the first co-primary endpoint.
- The 99% exact binomial confidence interval around the INSPIRE outcome (87.8% to 97.6%) provides an indication of conservative variability for eligible organs under standard of care with a lower bound about 6% away from the target.

- The lack of historical data and limited knowledge with respect to non-ideal donor lung transplantation suggests a 12% margin (i.e., doubling the lower bound distance of 6% associated with the INSPIRE estimate).

The formal statistical hypothesis test is as follows:

H_0: $\pi_{OCS\ Lung} \leq 0.819$

H_1: $\pi_{OCS\ Lung} > 0.819$

where $\pi_{OCS\ Lung}$ is the proportion of transplanted recipients alive Day 30 and at initial hospital discharge.

This co-primary effectiveness endpoint will be summarized using a count and percentage with an exact 95% confidence interval for the percentage based on the binomial distribution. A one-sided exact binomial test at the 0.025 significance level will be performed to test the null hypothesis H_0.

9.3.2. Co-primary Effectiveness Endpoint #2

The second co-primary hypothesis is that the Utilization Rate (defined in Section 4.1 above) is greater than a performance goal of 0.54 (54%), which is based on the utilization rate reported for XVIVO in the NOVEL Trial.[2] The formal statistical hypothesis test is as follows:

H_0: $\pi_{OCS\ Lung} \leq 0.54$

H_1: $\pi_{OCS\ Lung} > 0.54$

where $\pi_{OCS\ Lung}$ is the observed utilization rate in the EXPAND trial.

The appropriateness of the performance goal of 54% is based on the following:

- The 54% rate is the only published data available on utilization rate for non-ideal donor lungs.[56]
- The donor lung inclusion/exclusion criteria are similar to those used for the XVIVO NOVEL study. Where differences exist, they tend to make the donor lungs more challenging for EXPAND II vs NOVEL. For example:
  - EXPAND II will enroll DCD donors with any PaO_2/FiO_2 ratio, while the NOVEL study only included DCD donors with PaO_2/FiO_2 ratio $\geq$ 300 mmHg.
  - EXPAND II will include older donors (age > 55 years) while NOVEL did not have an inclusion criterion based on donor age. Donor age > 55 years old is known to have a negative impact on outcomes after lung transplantation.[4]
- Finally, this co-primary endpoint is designed to show superiority of the OCS™ Lung System to the XVIVO EVLP device. Demonstrating superiority to the only published data on utilization in the non-ideal donor lung population is a rigorous and appropriate test of a new technology.

This co-primary effectiveness endpoint will be summarized using a count and percentage with an exact 95% confidence interval for the true percentage based on the binomial distribution. A one-sided exact binomial test at the 0.025 significance level will be performed to test the null hypothesis, H_0.

9.4. Secondary Effectiveness Endpoints

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

9.5. Other Effectiveness Endpoints

These endpoints will be summarized using relevant descriptive statistics (e.g., mean, standard deviation, count, percentage, 95% CI).

9.6. Analysis of Safety

9.6.1. Primary Safety Endpoint

Safety will be analyzed principally by examination of the frequency of adverse events. In particular, the primary safety endpoint is the number of lung graft-related serious adverse events (SAEs) up to the 30-day follow-up or until initial hospital admission (if longer than 30 days) 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 (see Appendix 3):

- Biopsy proven moderate or severe acute rejection
- Respiratory failure requiring prolonged intubation or reintubation
- Bronchial anastomotic complications
- Major pulmonary-related infection

The primary safety hypothesis is that the mean number of lung graft-related SAEs up to the 30-day follow-up after transplantation is less than a performance goal based on the corresponding mean in the Per-Protocol population of the Control arm of the INSPIRE trial (0.29 events per subject) with a margin of 0.7 events. Specifically:

H_0: $\mu_{OCS\ Lung} \geq 0.99$

H_1: $\mu_{OCS\ Lung} < 0.99$

where $\mu_{OCS\ Lung}$ is the mean number of lung graft-related SAEs through 30 days post-transplantation among transplanted recipients.

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. A one-sided one-sample t-test at the 0.025 significance level will be performed to test the null hypothesis H_0.

9.6.2. Other Adverse Events

In addition, the numbers and percentages of subjects experiencing at least one lung graft-related AE, at least one severe AE, at least one device-related AE, at least one unanticipated AE, and at least one serious AE, and the number and percentage of deaths will all be tabulated.

The number of adverse events and the number and percentage of subjects experiencing adverse events will be tabulated by system organ class and preferred term using MedDRA. A similar analysis will be performed for serious AEs. The number and percentage of subjects experiencing AEs will also be tabulated by system organ class and preferred term and the relationship of the

adverse event to the device (focusing on differentiating adverse events deemed definitely and probably related to the device). Similar analyses will be performed by the severity of the adverse event.

9.7. Sample Size Determination

The sample size for this trial was determined based on providing adequate statistical power for hypothesis testing of the two co-primary effectiveness endpoints. All sample size calculations were performed using PROC POWER in SAS.

For the first co-primary endpoint, the calculations assumed a one-sided exact binomial test, an alpha level of 0.025, a control-based rate of 0.939 with a margin of 0.12 (to derive the performance goal of 0.819), a true survival rate for OCS™ of 0.939, and desired power of 90%. Based on these specifications, the required sample size was determined to be 84 transplanted recipients.

For the second co-primary endpoint, the calculations assumed a one-sided exact binomial test, an alpha level of 0.025, a performance goal of 0.54, a utilization rate of 72% for OCS™, and desired 90% power. Based on these specifications, the required sample size was determined to be 84 transplanted recipients

In order to ensure that a sufficient number of subjects are evaluable in the per-protocol population of the trial, 90 transplanted recipients in the study is expected to provide adequate power to evaluate the two co-primary effectiveness objectives given the assumptions described.

Due to multiple primary endpoints, the Hochberg Method[55] will be used to control familywise error. The p-values for each of the co-primary endpoints will be ordered from highest to lowest. If the highest p-value is less than 0.025 then both endpoints achieve statistical significance and the null hypothesis of each co-primary endpoint can be rejected. If not, then the lower of the two p-values will be assessed against a significance level of 0.0125. If the adjusted significance level of 0.0125 is applied to any of the co-primary endpoints, the power of that analysis will be greater than 85%. Therefore, the study will be considered successful in either of the two scenarios described above.

With regard to the primary safety endpoint, the pre-specified safety margin of 0.7 events per patient, the estimated mean of 0.29 events per patient (with an estimated standard deviation of 2.0), a one-sided alpha of 0.025, and the sample size of 90 transplanted recipients results in power greater than 90% when considering a one-sample t-test on the mean.

10. RISK ANALYSIS

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

10.1. Potential Risks

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

- **Potential Risks Associated with Lung Transplant Procedures**: These risks include post-operative complications, such as graft failure, primary graft dysfunction, rejection, infection and other organs/systems complications, graft vessel disease (an

expression of chronic rejection), infection, abnormal kidney function, diabetes, high level of cholesterol, high blood pressure, cancer and neurological complications.

- **The Potential Risk Associated with The Investigational Device:** As with any medical device, there is always a risk of extremely rare or previously unknown side effects developing from the treatment.
- **Potential Risk of Using a Donor Lung that is Unsuitable for Transplantation:** Regardless of the preservation system that is used, there is the risk that a patient can receive a lung that does not adequately function. This trial is designed to utilize lungs that would not be accepted for transplantation using cold storage preservation. There is the possibility that using such lungs may increase the risk of transplanting a lung that that does not function appropriately.

10.2. Manner in Which the Potential Risks Have Been Minimized

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

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

In addition, the OCS™ Lung System, Perfusion Module and Solution Set has been used clinically in more 50+ successful clinical transplants from conventional, high-risk and Donors after Cardiac Death (DCD) donor lungs with excellent post-transplant outcomes of 100% 30-day survival, 0% device malfunction and no organ loss based on device failure or any other reasons.[2,3]

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 lung acceptance criteria after OCS™ Lung System perfusion and assessment is designed based on the current international clinical standards of accepting conventional donor lungs for transplantation.[11] Thus, the donor lung will

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

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

10.3. Potential Benefits

The low utilization of donor lungs has led to a severe shortage of donor lungs to meet the large and growing need for lung transplantation; the Scientific Registry for Transplant Recipients (SRTR) and Organ Procurement Transplant Network (OPTN) report a ~20% mortality on the lung transplant waiting list in the U.S. In addition, they reported ~10% were removed from the waiting list due to deteriorating conditions and lack of suitable donors.

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

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

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

10.4. Risks Benefits Ratio

Based on the above, the benefits of using OCS™ Lung System technology to recruit, preserve and assess donor lungs to ensure their suitability for lung transplantation far outweigh any potential risks to the trial subjects.

11. DEVICE/SITE MANAGEMENT

11.1. Packaging and Labeling

The investigational device will be provided to the investigator(s) by the Sponsor. The Lung Perfusion Set and accessories and the OCS™ Lung Solution will be supplied sterile and are intended and labeled for single use.

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

11.2. Storage

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

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

11.3. Accountability

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

11.4. Device Complaints and Malfunctions

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

12. REGULATORY / ETHICS

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

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

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

12.2. Informed Consent

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

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

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

The approved written informed consent form will be signed and dated by the subject and the investigator 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 Informed consent form is provided in Appendix 5.

13. DATA COLLECTION/RECORDS/REPORTS

13.1. Investigator Records

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

- Investigator Certification/Agreement, signed by the principal investigator, that lists any co- or sub-investigators who will be involved in conducting the investigation under the direction of the principal investigator, and disclosure of any financial interest
- A copy of the principal investigator's curriculum vitae (CV), as well as copies of CVs for any co- and sub-investigators
- Written approval of the trial from the IRB or EC
- A copy of the approved informed consent document.

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

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

The investigator will not dispose of any records relevant to this trial without (1) written permission from the Sponsor and (2) providing an opportunity for the Sponsor to collect such records. The investigator will take responsibility for maintaining adequate and accurate

electronic or hard copy source documents of all observations and data generated during this trial. Such documentation is subject to inspection by the Sponsor and regulatory authorities.

13.2. Investigator Reports

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

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

13.3. Data Collection

During each subject assessment, an investigator participating in the trial will record progress notes to document all significant observations. In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes. For transmission to the Sponsor, information from the trial progress notes and other source documents will be promptly entered into the electronic database (eCRFs). Any changes to information in the trial progress notes, and other source documents, will be initialed and dated in ink on the day the change is made by a site trial staff member authorized to make

the change. Changes will be made by striking a single line through erroneous data, and clearly entering the correct data, e.g., ~~wrong data~~ right data. If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the clinician.

All data required by the trial protocol will be completely and accurately entered into the trial database by the investigator or his or her designate. The draft eCRFs are provided in Appendix 6.

13.4. Source Documents

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

13.5. Archiving of Records

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

13.6. Sponsor Records and Reports

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

14. CLINICAL MONITORING

14.1. Monitoring

A representative of the Sponsor will monitor the study on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations such as the objective, purpose, design, complexity, enrollment rate, size, and endpoints of the study.

Authorized representatives of TransMedics and/or regulatory authority representatives will conduct on-site visits to review, audit, and copy study-related documents. These representatives will meet with the investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions.

TransMedics or designee will monitor the investigation to ensure that it is conducted in accordance with the protocol and the following guidelines and standards: ISO 14155, the Code of Federal Regulations 21 CFR Part 812 and country specific regulations.

During the monitoring visits, the following documents must be made available for review: all CRFs, all source documents such as medical records and clinical charts and any other study related documents.

The details on the monitoring activities are detailed in the Monitoring Plan for the study.

14.2. Additional Auditing

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

14.3. Protocol Deviations

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

14.4. Clinical Events Committee

The Sponsor will utilize a Clinical Event Committee (CEC) composed of at least 3 lung transplant experts to provide blinded individual serious adverse event adjudication for the trial. It is anticipated that the CEC will meet with the Sponsor on a periodic basis, or as needed, depending on the rate of patient accrual. The primary responsibilities of the CEC are to:

- Review all adverse events reported over the course of the trial and the subsequent classification of these adverse events as related to the device or not and whether anticipated or unanticipated.
- Review donor and recipient treatment group eligibility issues.
- Validate donor lungs criteria: Review the donor lung characteristics, risk factors and retrieval conditions to assess whether each donated organ in this trial is considered non-ideal as defined in the inclusion criteria of this protocol
- Evaluate possible protocol deviations.
- Review and adjudicate all Primary Graft Dysfunction through 72 hours and all causes of death through initial hospitalization following transplantation
- Review and adjudicate causes of death in the trial

14.5. Data Safety Monitoring Board and 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 independent stopping rules below will be used in the study (violation of either rule warrants discontinuation of the study).

14.5.1. Mortality through Day 30 or Initial Hospital Discharge

Let p denote the true proportion of recipients transplanted with an OCS™-treated lung for whom the recipient does not survive until Day 30 or hospital discharge, whichever is later. Whenever a patient experiences this event, calculate a 97.5% lower confidence bound for p (exact binomial). Stop the study if this lower confidence bound exceeds 0.10 (10.0%).

Table 4 below shows the conditions under which the study would be stopped for a range of numbers of events (m) and a range of numbers of patients (n). The above stopping rule would, however, be applied to all combinations of number of events and number of patients observed in the study after a minimum of 20 patients are enrolled and transplanted with the OCS™. The letter "S" in a cell indicates that the study would be stopped if this condition were met. If the letter "C" appears, the study would continue. One sees, for example, that the study would be stopped if there were 6 events out of the first 20 patients or 8 events out the first 30 patients.

Table 4: Conditions under which the Study would be Stopped

	M																
n	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
20	C	C	C	C	C	S	S	S	S	S	S	S	S	S	S	S	S
30	C	C	C	C	C	C	C	S	S	S	S	S	S	S	S	S	S
40	C	C	C	C	C	C	C	C	S	S	S	S	S	S	S	S	S
50	C	C	C	C	C	C	C	C	C	S	S	S	S	S	S	S	S
60	C	C	C	C	C	C	C	C	C	C	C	S	S	S	S	S	S
70	C	C	C	C	C	C	C	C	C	C	C	C	S	S	S	S	S
80	C	C	C	C	C	C	C	C	C	C	C	C	C	C	S	S	S

TransMedics will be responsible for implementing the stopping rule.

14.5.2. PGD3 at 72 hours Post-transplant

Let p denote the true proportion of recipients transplanted with an OCS™-treated lung for whom the recipient experiences PGD3 at 72 hours post-transplant. Whenever a patient experiences this event, calculate a 97.5% lower confidence bound for p (exact binomial). Stop the study if this lower confidence bound exceeds 0.15 (15.0%).

Table 5 below shows the conditions under which the study would be stopped for a range of numbers of patients with events (m) and a range of numbers of patients (n). The above stopping rule would, however, be applied to all combinations of number of patients with events and number of patients observed in the study after a minimum of 20 patients are enrolled and transplanted with the OCS™. The letter "S" in a cell indicates that the study would be stopped if this condition were met. If the letter "C" appears, the study would continue. One sees, for example, that the study would be stopped if there were 7 patients with events out of the first 20 patients or 10 patients with events out the first 30 patients.

Table 5: Conditions under which the Study would be Stopped

n	m																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
20	C	C	C	C	C	C	S	S	S	S	S	S	S	S	S	S	S	S	S	S
30	C	C	C	C	C	C	C	C	C	S	S	S	S	S	S	S	S	S	S	S
40	C	C	C	C	C	C	C	C	C	C	C	S	S	S	S	S	S	S	S	S
50	C	C	C	C	C	C	C	C	C	C	C	C	C	S	S	S	S	S	S	S
60	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	S	S	S	S	S
70	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	S	S	S
80	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	S

TransMedics will be responsible for implementing the stopping rule.

14.6. Investigator Training

Device and database training will be provided to all the participant investigators and support staff prior to patient enrollment in the trial. Device training will be conducted at the TransMedics or equivalent training facility. 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. Device training will include the following:

- A didactic session, where the investigators will be introduced to the device and its use model through presentations and videos.
- Hands-on experience.

The Sponsor will perform animal procedures to train investigators on the device as follows:

- Device set-up, that includes system check, installation and priming of the Lung Perfusion Set.
- Lung instrumentation on the device that includes cannulation of the donor lung and subsequent instrumentation of the lung on the device. It also includes adjustment of different parameters such as gas flow rate, temperature and blood flow rate of the blood and solution perfusate as recommended in the IFU.
- Cessation of lung perfusion and removal from the device by using appropriate solutions and then terminating the circulatory pump.

15. INVESTIGATIONAL SITE TERMINATION

The Sponsor may terminate an investigational site from the study for any of the following reasons:

- Repeated failure to complete case report forms
- Failure to obtain Informed Consent
- Failure to report Serious Adverse Events

- Loss of or unaccountable investigational device inventory
- Repeated protocol violations
- Failure of investigator to comply with training or IFU
- Failure to follow patient management guidelines

16. CONFIDENTIALITY

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

17. AMENDMENT POLICY

The investigator will not make any changes to this plan without prior written consent from the Sponsor and subsequent approval by the IRB or EC, except if the deviation from the protocol is necessary to protect the life and physical well-being of a subject in an emergency. Such protocol deviations will be reported to the Sponsor and the reviewing IRB or EC as soon as possible, but no later than 5 working days after the emergency occurred.

Any permanent change to the protocol, whether it is an overall change or a change for specific trial center(s), will be handled as a protocol amendment. Any amendment to the protocol that appears indicated as the trial progresses will be fully discussed by the investigator(s) and the Sponsor. If agreement is reached regarding the need for an amendment, it will be written by the Sponsor. The written amendment will be submitted to the chairman of the IRB or EC responsible for reviewing amendments.

Except for "administrative letters," investigators will await IRB or EC approval of protocol amendments before implementing the change(s). Administrative letters are defined to have no effect on the validity of the data or information resulting from the completion of the approved protocol, or the relationship of likely patient risk to benefit relied upon to approve the protocol; the scientific soundness of the investigational plan or protocol; and, the right, safety or welfare of the human subjects involved in the investigation. The Sponsor will notify the FDA of such changes in a 5-Day Notice. When, in the judgment of the IRB or EC, the investigators and/or the Sponsor, the amendment to the protocol substantially alters the trial design and/or increases the potential risk to the subject; such changes will be approved by the FDA and the IRB and EC.

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

PGD Grading System (Christie, 2005, including caveat listed below)

Grade	PaO_2/FiO_2	Radiographic Infiltrates Consistent with Pulmonary Edema
0	>300	Absent
1	>300	Present
2	200–300	Present
3	<200	Present

We will use the ISHLT 2005 consensus statement of PGD. Specifically, PGD grade will be based on the following criteria:

1. If the patient is intubated, the PGD will be graded based on the above table.
2. If the patient was extubated, the PGD will be graded 0 or 1 based on absence or presence of infiltrates and/or edema on chest radiograph.
3. All ECMO use will be graded as grade 3 except for pre-specified center specific protocol ECMO for pulmonary hypertension and/or hemodynamic support.[1]

These criteria will be applied at the T0, 24, 48, and 72-hour timepoints after transplantation according to ISHLT guidelines.

PGD Assessment Timepoints Definition

PGD Assessment Timepoint	Definition
T0	At the time of ICU admission post-transplant
T24	24 hours post-transplant*
T48	48 hours post-transplant*
T72	72 hours post-transplant*
* Use closest value to these timepoints.	

[1] In addition, TransMedics will perform two additional exploratory analyses: (1) analyze the PGD results with patients on pre-specified center-specific ECMO excluded (ungradeable) and (2) analyze the PGD results with patients on pre-specified center-specific ECMO graded as PGD3.

APPENDIX 2. PATHOLOGIC GRADING OF LUNG REJECTION (MARTINU, 2009)

Category	Grade	Meaning	Appearance
A: Acute Vascular Rejection	A 0	None	Normal lung parenchyma
	A1	Minimal	Inconspicuous small mononuclear perivascular infiltrates
	A2	Mild	More frequent. More obvious, perivascular infiltrates, eosinophils may be present
	A3	Moderate	Dense perivascular infiltrates, extension into interstitial space, can involve endothelialitis, eosinophils, and neutrophils
	A4	Severe	Diffuse perivascular. Interstitial, and air-space infiltrates with lung injury. Neutrophils may be present.
B: Acute Airway Inflammation	B0	None	No evidence of bronchiolar inflammation
	B1R	Low grade	Infrequent, scattered or single layer mononuclear cells in bronchiolar submucosa
	B2R	High grade	Larger infiltrates of larger and activated lymphocytes in bronchiolar submucosa. Can involve eosinophils and plasmacytoid cells.
	BX	Upgradable	No bronchiolar tissue available

APPENDIX 3. PRIMARY SAFETY ENDPOINT

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

- **ACUTE REJECTION (Biopsy proven greater than grade A2):** Defined as moderate or severe according to the ISHLT working formulation of Pathologic grading listed in Appendix 1 of this protocol.
- **RESPIRATORY FAILURE:** Defined as Impairment of respiratory function requiring re-intubation, tracheostomy or the inability to discontinue invasive ventilator support within 4 days (96 hours) post-transplant. This excludes intubation for re-operation or temporary intubation for diagnostic or therapeutic procedures. (Slightly modified from Intermacs[2]).
- **BRONCHIAL ANASTOMOTIC COMPLICATION:** Defined as moderate to severe necrosis (mucosal and/or extending to bronchial wall) at the bronchial anastomotic site due to ischemic injury, with or without bronchial anastomotic dehiscence (Grade II – IV) as visualized by flexible fiber optic bronchoscopy and/or chest CT (for dehiscence), and/or requiring antibacterial/antifungal treatment, chest tube placement (tube thoracostomy), uncovered metallic stent placement, primary repair, open surgical repair, pneumonectomy, or re-transplantation. Bronchoalveolar (BAL) specimen/culture should be obtained if evidence of focal infection prior to initiating treatment. (Santacruz 2009, Van de Wauwer 2007).
- **MAJOR PULMONARY-RELATED INFECTION:** Defined as a clinical infection of lung origin that is treated with antibacterial/antifungal/antiviral agents (non-prophylactic). This category includes, but is not limited to: bacterial pneumonia/tracheobronchitis (*Pseudomonas aeruginosa*, coagulase-positive and coagulase-negative *Staphylococcus* species (including MRSA), *Chlamydia pneumoniae*, Enterococcus (including VRE), Enterobacteriaceae), Cytomegalovirus (CMV0 pneumonitis/pneumonia, Herpes Simplex Virus (HSV) tracheobronchitis/pneumonitis/pneumonia, Aspergillustracheobronchitis/pneumonia, and aspiration pneumonia/pneumonitis. Presence of pulmonary infiltrate(s) on chest x-ray along with a positive BAL specimen/culture, or positive sputum culture, or positive fungal staining/culture, and/or chest CT, and/or transbronchial biopsy specimen to confirm infection and rule out rejection should be present unless strong clinical evidence indicates the need for treatment despite negative cultures. CMV diagnosis requires BAL for cytology or transbronchial biopsy specimen. Diagnosis of Aspergillosis requires fungal histopathology and/or culture of BAL/tissue specimen, bronchoscopic findings consistent with the disease, and possible chest CT. Paradis 1993, Maurer 1992, Horvath 1993, Zamora 2004, Singh 2003, Silveira 2008, Lau 2004, Kotloff 2004).

Serious Adverse Event (SAE) Definitions:

[2] Intermacs (Interagency Registry for Mechanically Assisted Circulatory Support) http://www.intermacs.org/

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 patient re-hospitalization or prolongs initial 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.

APPENDIX 4. SCHEDULE OF CLINICAL ASSESSMENTS

Evaluations	Donor & Lung Assessments	
	At Acceptance	OCS Preservation
Eligibility & ID	X	
Demographics/Characteristics	X	
Donor Cause of Death	X	
Donor Medical History	X	
Initial & Final Blood Gas and PaO_2/FiO_2 Ratio at donor's offer	X	
Ventilation Settings at Final Blood Gas in donor's offer	X	
Final Chest X-ray report/findings	X	
Final Bronchoscopy Findings	X	
Cross Clamp Time and Flush Details		X
Donor Allocation Status		
OCS Pre-Instrumentation ABG (Priming)		X
OCS Instrumentation Details (Date and Time)		X
OCS Preservation Parameters		X
OCS Final Assessment		X
Device Malfunction (if applicable)		X
Non-transplant Reasons (if applicable)		X

Evaluations	Recipient Schedule of Assessments									
	Day of TX	T0	T24	T48	T72	Day 7	Discharge	Day 30	Mo 6	Mo 12, 24, & 36
Eligibility & Informed Consent	X									
Demographic/Characteristics	X									
Etiology of Lung Failure	X									
Medical History including Cardiac	X									
Transplant Details	X									
PGD Scores		X	X	X	X					
Mechanical Circulatory Support & Reason	X	X	X	X	X	X	X	X		
Invasive Ventilator Support	X	X	X	X	X	X	X	X		
Patient Survival								X	X	X
Graft Survival								X	X	X
Bronchoscopy, BAL & Biopsy							X		X*	X*
Pulmonary Function Test							X**		X*	X*
Immunosuppressive Meds & Induction (if applicable)	X					X	X			
ICU & Hospital Stay		X	X	X	X	X	X	X		
Lung Graft-Related SAE's	X	X	X	X	X	X	X	X		
All SAE's & Associated Meds	X	X	X	X	X	X	X	X		
Diagnosis of BOS									X	X

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

** Pulmonary Function Test can be done within the first 90 days post transplant according to patient's condition. If not done reason will specified and recorded.

APPENDIX 5. DRAFT PATIENT INFORMED CONSENT FORM TEMPLATE

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APPENDIX 6. DRAFT CASE REPORT FORMS

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