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Clinical Protocol and Investigational Plan

Continued Access Protocol to Evaluate the Effectiveness of the Portable Organ Care System (OCS™) Liver for Preserving and Assessing Donor Livers for Transplantation (OCS Liver PROTECT CAP)

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CONFIDENTIAL – PROPRIETARY INFORMATION

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OCS LIVER PROTECT CAP SYNOPSIS

Protocol Title	Continued Access Protocol (CAP) to Evaluate the Effectiveness of The Portable Organ Care System (OCS™) Liver for Preserving and Assessing Donor Livers for Transplantation (OCS Liver PROTECT CAP)
Objectives	To continue to evaluate the effectiveness of the OCS Liver System to preserve and assess donor livers having one or more of the following characteristics: • Donor age ≥ 40 years old; or • Expected cross clamp time ≥ 6 hours; or • Donor after circulatory death (DCD) with age ≤ 55 years old; or • Steatotic liver > 0% and ≤ 40% macrosteatosis at time of retrieval (on pre-retrieval histology).
Trial Design	Prospective, single arm, continued access protocol
Trial Size	A maximum of 21 participating sites to enroll 184 transplanted liver recipients
Screening and Treatment	• Primary Liver transplant candidates will be screened for trial eligibility. • Donor livers will be screened for trial eligibility. Eligible donor livers will be preserved using the OCS Liver System (OCS).
Donor Liver Eligibility Criteria	**Inclusion** Donor meets at least one of the following: • Donor age ≥ 40 years old; or • Expected total cross clamp time ≥ 6 hours; or • Donor after circulatory death (DCD) with age ≤ 55 years old; or • Steatotic liver > 0% and ≤ 40% macrosteatosis at time of retrieval (based on retrieval biopsy readout (only if the donor liver was clinically suspected to be fatty by the retrieval surgeon at time of liver retrieval). **Exclusion** Donor livers will be excluded if they meet any of the following criteria: • Living donors • Liver intended for split transplants • Positive serology (HIV, Hepatitis B surface antigen & Hepatitis C) • Presence of moderate or severe traumatic liver injury, or anatomical liver abnormalities that would compromise ex-vivo perfusion of the donor liver (i.e., accessory blood vessels or other abnormal anatomy that require surgical repair) and livers with active bleeding (e.g., hematomas) • Donor livers with macrosteatosis of > 40% based on retrieval biopsy readout.
Recipient Eligibility Criteria	**Inclusion** Recipients are required to meet all the following criteria on the day of transplant: • Registered primary Liver transplant candidate, male or female • Age ≥ 18 years old • Signed: (1) written informed consent document and (2) authorization to use and disclose protected health information. **Exclusion** Recipients will be excluded if they meet any of the following criteria on the day of transplant: • Acute, fulminant liver failure • Prior solid organ or bone marrow transplant • Chronic use of hemodialysis or diagnosis of chronic renal failure, defined as chronic serum creatinine of > 3 mg/dl for > 2 weeks and/or requiring hemodialysis • Multi-organ transplant • Ventilator dependent • Dependent on > 1 IV inotrope to maintain hemodynamics.
Primary Effectiveness	Incidence of Early liver Allograft Dysfunction (EAD) or primary non-function, defined as presence of one or more of the following criteria:

Endpoint	• AST level > 2000 IU/ml within the first 7 postoperative days; • Bilirubin ≥ 10 mg/dl on postoperative day 7; • INR ≥ 1.6 on postoperative day 7; or • Primary non-functioning graft within the first 7 days (defined as irreversible graft dysfunction requiring emergency liver re-transplantation or death, in the absence of immunologic or surgical causes).
Secondary Effectiveness and OCS Donor Liver Assessment Endpoints	• OCS donor liver assessment during perfusion, defined as, among donor livers preserved using OCS for the entire preservation period, the proportion of livers on which measurements of all of the following during perfusion will be available on OCS device before transplant o Lactate level (every two hours) o Average bile production rate (based on total bile production volume and duration of OCS perfusion) o Hepatic Artery Pressure (continuously) o Portal Vein Pressure (continuously) • Patient survival at Day 30 post-transplantation • Patient survival at initial hospital discharge post liver transplantation.
Other Endpoints	• Length of initial post-transplant ICU stay • Length of initial post-transplant hospital stay • Evidence of ischemic biliary complications diagnosed at 6 and at 12 months post-transplant • Extent of reperfusion syndrome as assessed based on the rate of decrease of lactate over the following timepoints: o During anhepatic phase immediately before reperfusion of the transplanted liver o 30-40 minutes after hepatic artery and portal vein reperfusion of the transplanted liver o 90-120 minutes after reperfusion of the transplanted liver • Pathology sample score for liver tissue samples taken at the following timepoints: o Donor liver pre-retrieval o Post-OCS preservation at the end of back preparation and immediately before the start of re-implantation o Post reperfusion 90-120 after reperfusion of the transplanted liver (prior to abdominal closure).
Safety Endpoints	Safety will be analyzed principally by examination of the frequency of liver graft-related serious adverse events (LGRSAEs) up to the 30-day follow-up after transplantation. This endpoint is defined as the average number of LGRSAEs through the 30 days post-liver transplantation per subject, consisting of the following serious adverse events (at most one per type per person): • Primary non-function (defined as irreversible graft dysfunction requiring emergency liver re-transplantation or death with the first 10 days, in the absence of immunologic or surgical causes) • Ischemic biliary complications (ischemic biliary strictures, and non-anastomotic bile duct leaks) • Vascular complications (liver graft-related coagulopathy, hepatic artery stenosis, hepatic artery thrombosis and portal vein thrombosis); • Liver allograft infections (liver abscess, cholangitis, etc.).
Follow-up	Patients will be followed for 24 months from the date of transplantation (some of which will be post-market). The following data will be collected at 6 and 12 months: • Patient and graft survival • Liver graft-related SAEs (6 months only) • Liver graft-related re-hospitalization after initial discharge, and, if yes, the primary reason/diagnosis for the hospitalization and the length of stay • Information will also be collected on any diagnosis of ischemic biliary complications and, if so, the method of diagnosis and treatment. The following data will be collected at 24 months: • Patient and graft survival. • Results of standard clinical practice or for cause liver biopsy will be collected (if applicable).
Analysis Populations	• The Per Protocol (PP) Population will consist of all subjects who are transplanted and have no major protocol violations and for whom the donor liver received the complete preservation procedure. The

	primary analysis of effectiveness and of secondary and other endpoints will be based on the PP Population. • The Modified Intent-to-Treat Population (mITT) will consist of all subjects who are transplanted. The mITT analyses will be considered secondary analyses of effectiveness. • The Donor Liver Population will consist of all donor livers which have preservation initiated using the OCS Liver System.
Effectiveness Analysis	The primary endpoint will be analyzed using the Per Protocol and mITT Populations. The Per Protocol analysis will be considered the primary analysis. Multiple imputation methods will be used for data imputation for any patients with missing values for this endpoint. Each secondary effectiveness endpoint will be summarized using counts and percentages and an exact 95% confidence interval for the true percentage based on the binomial distribution. The secondary effectiveness endpoints will be analyzed using the PP and the mITT Populations. The Per Protocol analysis will be considered the primary analysis.
Safety Analysis	The safety endpoints will be summarized using descriptive statistics. For livers that are not transplanted, the reason(s) for non-transplantation (including device failure) will be summarized using counts and percentages. The number and percentage of donor livers in the Donor Liver Population for which these was a device failure will also be presented.
Sample Size	184 subjects at up to 21 U.S. sites
Trial Sponsor	TransMedics, Inc. 200 Minuteman Road, Suite 302 Andover, MA, USA 01810

1. INTRODUCTION AND BACKGROUND

This Continued Access Protocol (CAP) is a continuation of the OCS Liver PROTECT trial which recently completed enrollment. The purpose of this study is to continue to evaluate the effectiveness of the OCS Liver System and collect additional clinical data from patients transplanted with donor livers preserved using the OCS Liver System while the marketing application for the OCS Liver System is being prepared and is under review at the FDA.

1.1. Background

Over the last two decades liver transplantation has evolved as the gold standard for treating end-stage liver failure disease and those with tumors of hepatic origin in the setting of liver dysfunction. The success of liver transplantation is now its primary obstacle, as the pool of donor livers fails to keep pace with the growing number of patients added to the national liver transplant waiting list. As of October 2019, there are over 13,000[1] patients listed on the U.S. national waiting list for liver transplantation, yet only 7,119 patients were transplanted in 2017 depriving thousands of patients of the gift of new livers to treat their end-stage liver disease. In addition, this significant discrepancy between supply and demand results in approximately 18% of patients either dying or becoming too sick to receive a liver transplantation (see Figure 1 below).

Figure 1: U.S. National Liver Transplant Waiting List Dynamics 2015-2017 Source: OPTN 2017/Scientific Registry of Transplant Recipients (SRTR) (Kim, et al., 2019).

Waiting list state	2015	2016	2017
Patients at start of year	14,622	14,037	13,703
Patients added during year	10,635	11,340	11,514
Patients removed during year	11,205	11,655	11,978
Patients at end of year	14,052	13,722	13,239

Removal reason	2015	2016	2017
Deceased donor transplant	6193	6903	7119
Living donor transplant	278	283	293
Transplant outside US	2	5	10
Patient died	1692	1413	1334
Patient refused transplant	92	121	115
Improved, transplant not needed	776	763	850
Too sick for transplant	1215	1194	1177
Other	957	973	1080

The current technique for liver preservation using cold flush and storage of donor livers plays a major role in the above large and growing clinical problem in liver transplantation. The current standard of care for donor liver preservation presents the following severe limitations:

- It subjects the donor livers to significant time-dependent ischemic injury (Zhai, et al., 2013; Wertheim, et al., 2011) and subsequent reperfusion injury that may impair liver function post-transplant. This causes transplanting physicians to select for procurement only those livers most likely to withstand the potential damage

[1] OPTN website, https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#

associated with cold storage preservation. It also imposes significant time and geographical limitations on the liver retrieval process, adversely impacting the utilization of available donor livers. In addition, this time-dependent ischemic injury has been directly correlated to post-transplant complications (Pan, et al., 2018).

- It lacks any perfusion capabilities to maintain the liver in a near-physiologic *(in- vivo-like)* environment after the donor liver is retrieved from the body of the donor (Vogel, et al., 2012). This limitation results in significant underutilization of the donor livers with fatty cells (macrosteatotic livers) and DCD livers. This further limits the use of these donor livers that otherwise are functioning normally in the body of the donor.
- It lacks any ability to evaluate organ metabolic state and function after procurement and preservation to determine the suitability of the donor livers for transplantation (Vogel, et al., 2012). This significantly limits the utilization of donor livers that are subjected to the negative, non-physiologic conditions of brain death in the donor and it severely limits the utilization of DCD livers.

1.2. Potential Clinical Solutions to Overcome Limitations in Donor Liver Utilization

Over the past 15+ years, there has been a global focus on *ex-vivo* organ perfusion in a near physiologic condition as a promising technique to overcome the current challenges in organ preservation and to potentially increase utilization of donor organs (liver, lung, heart, and kidney) that are currently not used due to shortcomings of cold storage (Olthoff, et al., 2010).

Isolated liver perfusion has been extensively studied for over 30+ years using a variety of different perfusates and perfusion temperatures. More recently, there has been an international focus in the liver transplant clinical and scientific community on normothermic liver perfusion using blood based perfusate to minimize the negative impacts of cold ischemic preservation on donor livers for transplantation. In addition, by maintaining livers in an active metabolic and functioning state, donor livers from heart beating or DCD donors can be assessed ex-vivo for suitability for transplantation.

The TransMedics' OCS Liver System technology is a portable system for ex-vivo perfusion and assessment of the donor livers for transplantation. The OCS Liver System maintains the donor liver in a metabolically active and functioning state (producing bile), by perfusing the liver with warm oxygenated and nutrient enriched blood-based perfusion solution. The OCS Liver System is intended to significantly reduce ischemia and reperfusion injuries on the donor livers and enable metabolic and functional assessment of donor livers to assess their suitability for transplantation. The OCS Liver System may enable the following clinical advantages:

- Reduction of the ischemia and reperfusion injuries on the donor livers during preservation, thus, eliminating the significant logistical and geographical barriers to Liver transplantation that currently exist with cold storage preservation.
- Optimization of donor liver ex-vivo environment by optimizing oxygen and substrate delivery, while also maintaining near normothermic condition to avoid the negative impact of cold temperature on fatty livers.

- Ex-vivo assessment of donor liver metabolic and functional state utilizing standard clinical tests of liver enzymes, bile production and lactate metabolism, enabling the transplanting clinical team to judge the suitability of the donor liver for transplantation and minimizing the risk of transplanting questionable donor livers into recipients.

In summary, there is a public health need for technologies, like the OCS Liver System, that can address the current shortcomings of the standard of care cold storage preservation for liver transplantation. Addressing the shortcomings of cold storage will allow increased utilization of donor livers, including fatty livers and DCD livers, and will help to overcome current geographical and logistical challenges to utilization of the existing donor pool. Enabling more liver transplants will help to address the disparity between the number of patients on the waiting list and the availability of donor livers.

1.3. Subject Enrollment and Health Insurance

Approximately 30-40% of liver transplant recipients have their care paid for by Medicare due to their age or disability status. Therefore, it is expected that Medicare patients will consent to participate in this study. Since Medicare patients in need of transplantation do not differ from transplant candidates receiving coverage from other payors, Medicare patients will be treated in the same manner as all other study Subjects and will realize the same potential benefits and risks experienced by all other Subjects in the study.

2. SUMMARY OF PRIOR TESTING AND INVESTIGATIONS

2.1. OCS Liver System Nonclinical Testing

The OCS Liver System is CE-marked and has undergone extensive preclinical testing to demonstrate its safety, effectiveness, and readiness for clinical use, before placement on the EU market. The Liver Perfusion Set has also been evaluated and tested in accordance with ISO-10993 “Biological Evaluation of Medical Devices.” These test results demonstrated that the device and its materials are biocompatible and suitable for their intended use. The Liver Perfusion Set will be provided sterile using validated methods, and is appropriately packaged to maintain sterility. The system 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 Liver System meets its expected performance specifications and is safe and suitable for clinical use.

Functional animal studies have demonstrated the safety, suitability, and performance of the OCS Liver System for preservation of donor livers.

2.2. OCS Liver PROTECT Study

The PROTECT Study is a prospective, pivotal, randomized study of the OCS Liver being conducted in the U.S. The objective of the study is to evaluate the effectiveness of the OCS to

preserve and assess donor livers intended for transplantation meeting current standard donor liver transplant acceptance criteria and one or more of the following characteristics:

- Donor age ≥ 40 years old;
- Expected total cross clamp/cold ischemic time ≥ 6 hours; or
- Donor after Cardiac Death (DCD donor) with age ≤ 55 years old; or
- Steatotic liver > 0% and ≤ 40% macrosteatosis at time of retrieval (based on retrieval biopsy readout (only if the donor liver was clinically suspected to be fatty by the retrieval surgeon at time of liver retrieval)).

The control group received donor livers meeting the same inclusion/exclusion criteria that were preserved using standard of care static cold storage. The PROTECT study is on-going and data are still being collected and no statistical analyses have been performed. The PROTECT study data has been periodically reviewed by an independent Data Safety Monitoring Board (DSMB) and no study concerns have been identified.

3. DEVICE DESCRIPTION

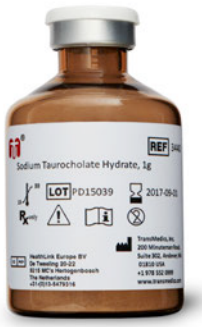
The OCS Liver System is an integrated portable platform designed to maintain donor livers in a near physiologic, normothermic perfused state. The OCS Liver System consists of:

- **The Portable Console & Monitor:** This is a compact electromechanical device that contains an integrated pulsatile perfusion pump, batteries, blood warmer, pressure, flow and saturation meters. In addition, it has an integrated wireless monitor that allows the clinical operator to control and display critical perfusion parameters of the preserved donor livers.
- **Single Use Sterile Perfusion Set:** At the core of the OCS Liver System is a sterile, biocompatible perfusion module that maintains the organ's physiologic environment and has embedded sensors to optimize and monitor the Liver perfusion parameters and bile production. In addition, the perfusion module enables perfusate sampling in order to monitor the liver's metabolic condition.
- **OCS Liver Bile Salts:** This is sodium taurocholic acid used for infusion to the circulating perfusate to replenish bile salt levels in the circulating perfusate during ex-vivo perfusion on the OCS Liver System.

A detailed description of the device can be found in the OCS Liver System Instructions for Use.

Figure 2: OCS Liver System

OCS Liver Console	OCS Liver Perfusion Set	OCS Liver Bile Salts

		
Note: The Liver Console figure (left) shows the LvPM mounted onto the system. The LvPs figure (middle) only shows the LvPM components of the LvPS.		

4. TRIAL OBJECTIVES

To evaluate the effectiveness of the OCS Liver System to preserve and assess donor livers having one or more of the following characteristics:

- Donor age ≥ 40 years old; or
- Expected cross clamp time ≥ 6 hours; or
- Donor after circulatory death (DCD) with age ≤ 55 years old; or
- Steatotic liver > 0% and ≤ 40% macrosteatosis at time of retrieval (on pre-retrieval histology).

4.1. Type of Trial

A prospective, multi-center, single arm Continued Access Protocol.

4.2. Trial Size and Subject Follow-up

This trial will enroll up to 184 transplanted recipients at up to 21 sites in the U.S. All subjects will be followed for 24 months from the date of transplantation (some of which will be post-market). The summary of the follow-up is in Appendix 2 of this document.

5. TRIAL ENDPOINTS

5.1. Primary Effectiveness Endpoint

Incidence of Early Liver Allograft Dysfunction (EAD) or primary non-function, defined as presence of one or more of the following criteria:

- AST level > 2000 IU/ml within the first 7 postoperative days;
- Bilirubin ≥ 10 mg/dl on postoperative day 7;
- INR ≥ 1.6 on postoperative day 7; or

- Primary non-functioning graft within the first 7 days (defined as irreversible graft dysfunction requiring emergency liver re-transplantation or death, in the absence of immunologic or surgical causes).

5.2. Secondary Effectiveness and OCS Donor Liver Assessment Endpoints

- OCS donor liver assessment during perfusion, defined as, among donor livers preserved using OCS for the entire preservation period, the proportion of livers on which measurements of all of the following during perfusion will be available on OCS device before transplant:
  - Lactate level (every two hours)
  - Average bile production rate (based on total bile production volume and duration of OCS perfusion)
  - Hepatic artery pressure (continuously)
  - Portal vein pressure (continuously)
- Patient survival at Day 30 post-transplantation
- Patient survival at initial hospital discharge post liver transplantation.

5.3. Other Endpoints

- Length of initial post-transplant ICU stay
- Length of initial post-transplant hospital stay
- Evidence of ischemic biliary complications diagnosed at 6 and at 12 months post-transplant
- Extent of reperfusion syndrome as assessed based on the rate of decrease of lactate over the following timepoints:
  - During anhepatic phase immediately before reperfusion of the transplanted liver
  - 30-40 minutes after hepatic artery and portal vein reperfusion of the transplanted liver
  - 90-120 minutes after reperfusion of the transplanted liver
- Pathology sample score for liver tissue samples taken at the following timepoints:
  - Donor liver pre-retrieval
  - Post-OCS preservation at the end of back preparation and immediately before the start of re-implantation
  - 90-120 minutes after reperfusion of the transplanted liver (prior to abdominal closure).

5.4. Safety Endpoint

Safety will be analyzed principally by examination of the frequency of liver graft-related serious adverse events (LGRSAEs) up to the 30-day follow-up after transplantation. This endpoint is defined as the average number of LGRSAEs through the 30 days post-liver transplantation per subject, consisting of the following serious adverse events (at most one per type per person):

- Primary non-function (defined as irreversible graft dysfunction requiring emergency liver re-transplantation or death with the first 10 days, in the absence of immunologic or surgical causes)
- Ischemic biliary complications (ischemic biliary strictures, and non-anastomotic bile duct leaks)
- Vascular complications (liver graft-related coagulopathy, hepatic artery stenosis, hepatic artery thrombosis and portal vein thrombosis)
- Liver allograft infections (liver abscess, cholangitis, etc.).

6. TRIAL POPULATION

The trial will include 184 Liver transplant recipients at up to 21 sites in the U.S.

6.1. Donor Eligibility Criteria

6.1.1. Donor Inclusion Criteria

Donor liver meets at least one of the following:

- Donor age ≥ 40 years old; or
- Expected total cross clamp time ≥ 6 hours; or
- Donor after circulatory death (DCD) with age ≤ 55 years old; or
- Steatotic liver > 0% and ≤ 40% macrosteatosis at time of retrieval (based on retrieval biopsy readout only if the donor liver was clinically suspected to be fatty by the retrieval surgeon at time of liver retrieval).

6.1.2. Donor Exclusion Criteria

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

- Living donors
- Liver intended for split transplants
- Positive serology (HIV, Hepatitis B surface antigen & Hepatitis C)
- Presence of moderate or severe traumatic liver injury, or anatomical liver abnormalities that would compromise ex- vivo preservation of the donor liver (i.e., accessory blood vessels or other abnormal anatomy that require surgical repair) and livers with active bleeding (e.g., hematomas)

- Donor livers with macrosteatosis of > 40% based on retrieval biopsy readout.

6.2. Recipient Eligibility Criteria

6.2.1. Recipient Inclusion Criteria

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

- Registered primary liver transplant candidate, male or female
- Age ≥ 18 years old
- Signed: (1) written informed consent document and (2) authorization to use and disclose protected health information.

6.2.2. Recipient Exclusion Criteria

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

- Acute, fulminant liver failure
- Prior solid organ or bone marrow transplant
- Chronic use of hemodialysis or diagnosis of chronic renal failure, defined as chronic serum creatinine of > 3 mg/dl for > 2 weeks and/or requiring hemodialysis
- Multi-organ transplant
- Ventilator dependent
- Dependent on > 1 IV inotropic support to maintain hemodynamics.

7. PRE-OPERATIVE TRIAL PROCEDURES

7.1. Subject Identification

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

7.2. Recipient Day of Transplant Assessment

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

- **Eligibility:** Investigator will review and confirm that the potential consented recipient continues to meet <u>all</u> inclusion criteria and <u>no</u> exclusion criteria.
- **Demographics/Characteristics:**

  - Date of birth or Age
  - Gender, body mass index
  - Race and Ethnicity
  - Blood type and RH factor
  - Recipient Model for End-stage Liver Disease (MELD) Score
  - Recipient ID
- **Baseline Liver Function Tests:**
  - Bilirubin levels
  - Aspartate aminotransferase (AST)
  - Alanine aminotransferase (ALT)
  - Gamma-glutamyl transpeptidase (GGT)
  - Alkaline phosphatase
  - International normalized ratio (INR)
  - Serum Lactate level
- **Recipient Risk Factors & Medical History:**
  - Indication for transplantation: The primary etiology of Liver failure will be recorded
  - History of Hepatitis C
  - History of liver cancer
  - History of diabetes.

7.3. Donor Screening and Acceptance

The investigator or a member of her/his transplant team will evaluate the donor and the quality and suitability of the liver for transplantation and for enrollment in the trial. The following evaluations will be conducted and recorded:

- **Organ Donor Identification Number** (i.e., UNOS Donor ID)
- **Demographics:** Age, Date of birth (if available), gender, race, and ethnicity
- **Donor Characteristics:** Blood type & RH factor, body mass index
- **Donor's Cause of Death:**
  - Cause of death and date and time of pronouncement of brain death
  - If the donor is a DCD donor, total time in minutes from discontinuation of support to cardiac stand still
- **Medical History:**

  - Active infection, positive serology for CMV, HIV, Hepatitis B or C, malignant tumors, and Liver disease
  - History of diabetes (if available)

- **Donor Liver Assessment:** The donor Liver will be assessed prior to procurement and acceptance using the following methods:
  - **Liver Enzymes:** the following tests will be collected if available:
    - Bilirubin levels;
    - Aspartate aminotransferase (AST);
    - Alanine aminotransferase (ALT);
    - Gamma-glutamyl transpeptidase (GGT);
    - Alkaline phosphatase;
    - International normalized ratio (INR);
    - Lactate level.
  - **Liver Biopsy** (see Appendix 1 of this document)**:** A needle biopsy will be collected from all donor livers at time of retrieval at time of cross clamp in the donor. Only donor livers that are clinically suspected to be fatty by retrieval team visualization, will require a pre-retrieval biopsy readout to estimate the degree of macrosteatosis and confirm eligibility (> 0 and ≤ 40% macrosteatosis).
- **Eligibility:** The donor will be evaluated to document whether the eligibility criteria are met. Any other clinical reasons for not accepting donor liver at final assessment before retrieval will be recorded.

7.4. Donor Liver Retrieval and OCS Preservation and Assessment

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

- **Initial Liver Flush in Donor Body:** All donor livers will be flushed using cold Belzer UW® solution or Custodiol® HTK preservation solutions according to the institution's standard of care practice and the manufacturer instruction for use.
- **OCS Liver Back Table Flush:** All donor livers will be flushed on the back table using cold PlasmaLyte® solution supplemented with sodium bicarbonate (NHCO3) 10 mml/L, Epoprostenol Sodium 2 mics/L, and Methylprednisolone ~160 mg/L flush below, according to the following protocol:
  - **Hepatic Artery:** 1 liter flush at ~50-70 mmHg pressure bag
  - **Portal Vein:** 2 liters gravity drain
- **OCS Liver Perfusion:** The OCS Liver System will be primed using the following

OCS Liver Perfusate Composition	Recommended Dose
Packed Red Blood Cells (pRBCs)*	4-8 units
Albumin 25%	400 mls

OCS Liver Perfusate Composition	Recommended Dose
PlasmaLyte® solution	700-800 mls
Methylprednisolone	500 mgs
Dexamethasone	20 mgs
Sodium Bicarbonate (NaHCORR$_3$RR) 8.4%	70 mmol
Adult Multivitamins for infusion e.g., INFUVITE®	1 unit
Calcium Gluconate 10% (100 mg/ml)	10 mls
Antimicrobials:	
Gram positive antibiotic e.g., Cefazolin	1 gm
Gram negative antibiotic e.g., Cirprofloxacin	100 mg
* type specific (or O negative blood group), , leukocyte reduced	

- **OCS Liver Perfusion Additives:** In addition to the above OCS Liver perfusate, the following will be infused to the perfusate mix using an ex-vivo solution pump:

OCS Liver Perfusate Additives	
Continuous Infusion Mix	**Dose**
Total parenteral nutrition (TPN) Mix: *CLINIMIX E TPN (4.25% Amino Acid / 10% Dextrose); PLUS* *Insulin 30 IU* *Glucose 25 gms* *Heparin 40,000 units*	30 ml/hr
As Needed Additives	**Dose**
Prostacyclin infusion as needed to control Hepatic artery pressure e.g., Epoprostenol Sodium 0.5 mg	0-20 mics/hr
Bile Salts e.g., Taurocholic acid sodium (1 gm/50 ml)	3 ml/hr
NaHCORR$_3$RR 8.4% to correct metabolic acidosis	1.5 meq/1 base excess

- **Bile Salt Preparation:** All study sites will be provided sealed Gamma-sterilized vials of 1 gm of Taurocholic acid sodium in salt form to be mixed prior to retrieval according to the following steps:

- Add 50 ml of sterile water for injection using aseptic technique
- Mix well to ensure all salt is dissolved.

At the time of use the OCS operator will spike the stopper of the vial using a sterile OCS infusion line and connect to the OCS infusion delivery system.

- **The OCS Liver Preservation Parameters:** Donor livers will be perfused on the OCS Liver System with OCS parameters maintained within the following ranges
  - Hepatic Artery Pressure (mean HAP): 75-100 mmHg
  - Hepatic Artery Flow (HAF): 300-700 ml/min
  - Portal Vein Pressure (mean PVP): 4-8 mmHg
  - Portal Vein Flow (PVF): 700-1700 ml/min
  - Perfusate Temperature (Temp): 34°C
  - Oxygen gas flow 400-700 ml/min
  - Circulating arterial Lactate (Lact) trend: trending down over time.

- **Lactate and Liver Enzyme Levels During OCS Liver Perfusion Sampling Scheme**: The organ retrieval team will collect samples from the arterial port of the OCS perfusion circuit to measure lactate level using a standard blood analyzer according to the following protocol:
  - OCS Baseline arterial sample within the first 10-30 min of liver instrumentation.
    - Lactate
    - Liver enzymes: AST, ALT, GGT, total bilirubin, and ALP.
  - Lactate samples will continue to be collected from the device at approximately hourly intervals until lactate level is trending down, at this time, lactate samples should be done every 2 hours or after any active HAF or HAP adjustments.
  - OCS Final arterial sample before cooling liver on OCS
    - Lactate
    - Liver enzymes: AST, ALT, GGT, total bilirubin, and ALP.
- **Final Liver Cooling and Flush Arrest on OCS:** all donor livers on OCS will be cooled and flushed on the OCS using cold PlasmaLyte® solution supplemented with sodium bicarbonate (NHCO3) 10 mml/L, Epoprostenol Sodium 2 mics/L, and Methylprednisolone ~160 mg/L flush below, according to the following protocol:
  - **Hepatic Artery:** 1 liter flush at ~50-70 mmHg pressure bag
  - **Portal Vein:** 2 liters gravity drain.
- **Liver Biopsy (see** Appendix 1**):** a needle biopsy will be collected from donor livers preserved on OCS on the back table, post-preservation, immediately before re-implantation.

- **OCS Preservation Information:** the following information will be collected
  - Device Information (serial number, etc.)
  - Device Malfunction(s)
  - OCS system data collected by the device during the preservation run and uploaded into the EDC database.
- **Donor Retrieval Details:** The following information will be collected at time of Liver retrieval
  - Date and time of cross clamp of donor aorta.
- **OCS Details (Liver Instrumentation details):**
  - Total cold ischemia time between initial donor cross clamp and start of OCS Liver perfusion.
- **OCS Parameters and Enabled Measurements:** The following OCS Liver perfusion parameters and Liver metabolic conditions will be recorded:
  - HAP
  - HAF
  - PVP
  - PVF
  - Total Bile volume
  - OCS Liver arterial lactate level.

7.5. Donor Liver Acceptance for Transplantation following OCS Liver Preservation

All donor livers that are preserved on the OCS Liver System are expected to be transplanted into a matching consented recipient. Any decision to turn down livers after they have been retrieved and preserved on OCS Liver System should be done with notification to the Site PI and the donor liver examined by the transplant center's qualified liver transplant pathologist and/or tissue slides/samples to be sent to core lab for the study for further examination. All reasons for turning down a donor liver after it has been preserved on the OCS Liver System will be collected in the eCRFs.

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

8.1. Transplant Details

The following information concerning the transplant procedure will be collected:

- The organ recipient unique post-transplant patient identifier

- Total cross clamp duration in minutes (from donor cross-clamp application to removal of cross-clamp in the recipient)
- Total cold ischemia time will be collected (OCS = cold ischemic time pre and post OCS Liver perfusion)
- Any surgical complications encountered during surgery
- Use of circulatory bypass will be recorded
- Type of liver anastomosis
  - Bicaval anastomosis; or
  - Piggyback anastomosis
- The total amount of any blood product and clotting factors transfusion will be collected (pRBCs, Fresh Frozen Plasma (FFP), platelets, etc.)
- Any inotropic support needed to maintain hemodynamics will be collected
- A liver tissue biopsy will be collected from the right lobe of the transplanted liver immediately before abdominal closure in the recipient. The biopsy will be collected according to Liver Biopsy protocol in Appendix 1.

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

- **Early Liver Allograft Dysfunction (EAD) Surveillance in the first 7 days:**
  - AST level > 2000 IU/ml within the first 7 postoperative days;
  - Bilirubin ≥ 10 mg/dl on postoperative day 7;
  - INR ≥ 1.6 on postoperative day 7; or
  - Primary non-functioning graft within 7days.
- **Inotropic Support to Maintain Hemodynamics at T0, T24 and T48 and T72 hours after ICU admission (if applicable) will be collected**
- **Initial use of Mechanical Respiratory Support:** Duration of initial post-transplant invasive ventilator support will be recorded from the time of initial admission to ICU post-Liver transplant until extubation.
- **Initial Post-Transplant ICU Stay:** Intensive care unit (ICU) admission time, and date and time when clinical order for ICU discharge is written.
- **Renal Replacement Therapy:** Need for dialysis treatments in the first 10 days post liver transplantation for patients that did not have renal replacement prior to transplantation
- **Immunosuppression Medications:** The type of immunosuppression medication and dose will be recorded at day 7 and at time of discharge from the hospital. Immunosuppression induction will be recorded if applicable.

- **Patient and Graft Survival at Day 30 and At Initial Hospital Discharge:** Patient and graft survival will be assessed on day 30 post-transplant and at initial hospital discharge post-liver transplantation.
- **Liver graft-related Serious Adverse Events:** All liver graft-related serious 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 liver graft-related adverse event (SAE)-related will be recorded in the trial electronic database until the SAE is resolved.

These follow-ups will be attempted within ± 3 days of the designated periods except for the Early Liver Allograft Dysfunction (EAD) Surveillance, in the first 7 days which must be collected at the designated times. The evaluations may be conducted over several days.

8.3. Long-term Follow-up: 6 and 12 & 24 Months

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

8.3.1. 6 and 12-Month Follow-up

At approximately 6- and 12-months post-transplant, the patient will be evaluated at an office visit if this is the institution's standard of care, and, if not, by phone contact by the site. The patient's medical record may be reviewed to confirm patient's answers. This follow-up will collect information on:

- Patient and graft survival
- Liver graft-related SAEs (6 months only)
- Liver graft-related re-hospitalization after initial discharge, and, if yes, the primary reason/diagnosis for the hospitalization and the length of stay
- Information will also be collected on any diagnosis of ischemic biliary complications and, if so, the method of diagnosis and treatment.

The 6 and 12-month follow-up will be collected within ± 1 month of the designated period and will be recorded on the 6- and 12-month follow-up electronic form.

8.3.2. 24-Month Follow-up

At approximately 24 months post-transplant (± 1 month), the patient will be evaluated at an office visit if this is the institution's standard of care, and, if not, by phone contact by the site. The patient's medical record may be reviewed to confirm patient's answers. This follow-up will collect information on:

- Patient and graft survival
- Results of standard clinical practice or for cause liver biopsy will be collected (if applicable).

The 24-month follow-up will be collected within ± 1 month of the designated period and will be recorded on the 24-month follow-up electronic form.

9. EVALUATION OF ADVERSE EVENTS

9.1. Evaluation of Liver Graft-Related Adverse Events (LGRAEs)

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

9.2. Serious Adverse Events (SAEs)

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

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

Only liver graft-related SAEs will be followed until their resolution.

9.3. Anticipated and Unanticipated Adverse Events

The investigator will assess each adverse event for whether it is anticipated or unanticipated. An unanticipated adverse event is defined as any adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with, a device if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the safety, or welfare of subjects.

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

- Acute rejection
- Atrial and ventricular arrhythmias
- Bleeding
- Hemodynamic instability
- Death
- Fever
- Early liver allograft dysfunction (EAD)
- Respiratory failure

- Liver primary non-function
- Bile leaks
- Hepatic artery thrombosis
- Portal vein thrombosis
- Cholangitis
- Liver abscess
- Diaphragmatic injury
- Phrenic nerve injury
- Sepsis
- Renal dysfunction and/or failure
- Hyperammonaemia
- Malignancy (post-transplant lymphoproliferative disorder (PTLD)
- Multiple organ failure
- Myocardial infarction
- Neurological dysfunction
- Hepatic dysfunction
- Diabetes due to steroid and anti-rejection medications
- Pancreatitis
- Peptic ulceration
- Gastritis
- Gastro esophageal reflux disease (GERD)
- Aspiration
- Cardiac tamponade
- Pneumo-mediastinum
- Pneumothorax
- Hemothorax
- Ascites
- Pleural effusion
- Venous thromboembolism (deep venous thrombosis [DVT])
- Pulmonary embolism (PE)
- Abdominal wound dehiscence
- Organ deemed not transplantable after retrieval
- Stroke
- Psychosis
- Ileus
- Bowel obstruction
- GI Bleeding (upper or lower)
- Cerebrovascular accident
- Peripheral vascular clotting or occlusion due insertion of mechanical support or equivalent
- Delirium, confusion and neurological complications
- Hepatic coma
- Retransplantation
- Limb gangrene due to vascular occlusion due insertion of mechanical support
- Use of mechanical circulatory support
- Coagulopathy
- Blood product transfusion
- Transfusion reaction
- Hyperacute rejection
- Anastomotic site complications; narrowing, bleeding or occlusion
- Bowel thromboembolic complications and gangrene
- Protamine and other anti-heparin medication reaction
- Heparin induced thrombocytopenia

9.4. Unanticipated Adverse Device Effect (UADE)

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

9.5. Recording and Reporting of Adverse Event

All liver graft-related adverse events and serious adverse events are to be captured until post-transplant day 30 or until initial hospital discharge, whichever comes first. 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 liver graft-related serious adverse events occurring during the course of the first 30 days post-transplant will be reported to TransMedics, Inc., as well as documented on the appropriate electronic case report form(s). For all liver graft-related SAEs, the investigator is required to supply any additional data that may be deemed necessary by the Sponsor. Additionally, any serious adverse events (SAE) and unanticipated adverse device effects (UADE) should be reported to TransMedics, Inc., as soon as possible after the investigator learns of the event. LGRAEs will be recorded up to the 30-day follow-up or through hospital discharge only if longer than 30 days. For any particular patient, the CEC, if required to protect patient safety, may specify a different follow-up period. The Sponsor is responsible for the classification and reporting of liver 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.

9.6. Relationship of an Adverse Events (AEs) to OCS Liver System

The investigator will assess the relationship of the Adverse Event (AE) to the OCS Liver System. The relationship will be assessed using the following categories:

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

9.7. 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.

9.8. Pre-Existing Conditions

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

10. STATISTICAL METHODS

10.1. General

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

All statistical procedures will be performed using SAS Version 9.3 or higher.

10.2. Analysis Populations

10.2.1. Per Protocol Population

The Per Protocol (PP) Population will consist of all subjects who are transplanted and have no major protocol violations and for whom the donor liver received the complete preservation procedure. The major protocol violations that will exclude a subject from this population are the following:

- 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, secondary or safety endpoints
- Other major protocol violations.

The primary analysis of effectiveness and of secondary and other endpoints will be based on the PP Population.

10.2.2. Modified Intent-to-Treat Population

The Modified Intent-to-Treat Population (mITT) will consist of all subjects who are transplanted. The mITT analyses will be considered secondary analyses of effectiveness. The safety analysis will also be based on the mITT population.

10.2.3. Donor Liver Population

The Donor Liver Population will consist of all donor livers which have preservation initiated using the OCS Liver System.

10.3. Data Analysis

The statistical analysis plan (SAP) will provide details on the statistical methods planned for this study and will be finalized prior to the database lock. Statistical summaries described in the sections below will primarily be provided for all subjects (i.e., overall summary) in the analysis populations of interest unless otherwise stated.

10.3.1. Subject Disposition

Subject disposition will be summarized and presented for the number and percentage of subjects who were enrolled, screen failures, completed the study, and discontinued early (including reasons for discontinuations).

10.3.2. Major Protocol Deviations

Major protocol deviations will be identified and documented based on a review of potential deviations. The potential major protocol deviations will be identified before database lock, either through programmatic checks of study data (e.g., inclusion/exclusion criteria violations), as well as through review of selected data listings (e.g., site-entered comments). The potential major protocol deviations to be reviewed include, but are not limited to, subjects who did not meet inclusion/exclusion criteria or eligibility was not adequately verified.

Individual major protocol deviations will be presented in a data listing. The number and percentage of subjects with major protocol deviations will be summarized by the type of deviations.

10.3.3. Demographics and Baseline Characteristics

Demographics, including (age, gender, race, and ethnicity where applicable), and other baseline characteristics collected at screening, such as height, weight, body mass index will be summarized using descriptive statistics. These data will be presented as a listing.

10.3.4. Primary Effectiveness Endpoint

The primary effectiveness endpoint for this study is the incidence of Early Liver Allograft Dysfunction (EAD) or primary non-function, defined as presentation of one or more of the following criteria:

- AST level > 2000 IU/ml within the first 7 postoperative days;
- Bilirubin ≥ 10 mg/dl on postoperative day 7;
- INR ≥ 1.6 on postoperative day 7; or
- Primary non-functioning graft within the first 7 days.

This endpoint will be analyzed using the Per Protocol and mITT Populations. The Per Protocol analysis will be considered the primary analysis.

Subgroup analyses of the primary effectiveness endpoint will be performed for the following subgroups of patients:

- DCD (donation after circulatory death) patients
- Fatty liver patients
- Donor Age
- Recipient with MELD > 30.

No data imputation or statistical tests will be performed for these subgroup analyses.

10.3.5. Secondary Effectiveness and OCS Donor Liver Assessment Endpoints

The secondary effectiveness endpoints for this trial are as follows:

- OCS donor liver assessment during perfusion, defined as, among donor livers preserved using OCS for the entire preservation period, the proportion of livers on which measurements of all of the following during perfusion will be available on OCS device before transplant
  - Lactate level (every two hours)
  - Average bile production rate (based on total bile production volume and duration of OCS perfusion)
  - Hepatic artery pressure (continuously)
  - Portal vein pressure (continuously)
- OCS Measurements during organ perfusion
- Patient survival at Day-30 post-transplantation
- Patient survival at time of initial hospital discharge post-transplantation.

These endpoints will be analyzed using the Per Protocol and mITT Populations, with the Per Protocol analysis being considered the primary analysis. Multiple imputation methods will be used for data imputation for patients with missing values for these endpoints.

Subgroup analyses of the secondary endpoints will be performed for the same subgroups of patients as for the primary effectiveness endpoint. No data imputation or statistical tests will be performed for these subgroup analyses.

10.4. Analysis of Safety

Safety will be analyzed principally by examination of the frequency of liver graft-related serious adverse events (SAEs) up to the 30-day follow-up after transplantation. This endpoint is defined as the average number of liver graft-related serious adverse events through the 30 days post-liver transplantation per subject, consisting of the following serious adverse events (at most one per type per person):

- Primary non-function (defined as irreversible graft dysfunction requiring emergency liver re-transplantation or death within the first 10 days, in the absence of immunologic or surgical causes)
- Ischemic biliary complications (ischemic biliary strictures, and non-anastomotic bile duct leaks)
- Vascular complications (liver graft-related coagulopathy, hepatic artery stenosis, hepatic artery thrombosis and portal vein thrombosis)
- Liver allograft infections (liver abscess, cholangitis, etc.).

In addition, the numbers and percentages of subjects experiencing at least one liver graft-related AE, at least one (definitely or probably-related) device-related AE, at least one unanticipated AE, and at least one serious AE, and the number and percentage of deaths will all

be tabulated. Also, the number of liver graft-related adverse events and the number and percentage of subjects experiencing liver graft-related adverse events will be tabulated by system organ class and preferred term using MedDRA. A similar analysis will be performed for LGRSAEs. AEs will also be tabulated at the event level by system organ class and preferred term and the relationship of the adverse event to the device using counts and percentages. Similar analyses will be performed by the severity of the adverse event.

For livers that are not transplanted, the reason(s) for non-transplantation (including device failure) will be summarized using counts and percentages. The number and percentage of donor livers in the Donor Liver Population for which these was a device failure will also be presented.

10.5. Sample Size Determination

The sample size for this CAP was determined based on the rate of enrollment in the PROTECT trial. The maximum number of patients enrolled is 184.

10.6. Statistical Analysis Plan

A formal statistical analysis plan will be prepared and finalized prior to data lock.

10.7. Stopping Rule

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

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

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

Table 1: Conditions under which Study Would Be Stopped

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

TransMedics will be responsible for implementing the stopping rule and will notify the DSMB as if the stopping rules are met. In addition, the DSMB will review the rules at the scheduled DSMB meetings.

11. RISK ANALYSIS

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

11.1. Potential Risks

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

- **Potential Risks Associated with Liver Transplant Procedures:**

  Potential risks associated with any liver transplant procedure 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), abnormal kidney function, diabetes, high level of cholesterol, high blood pressure, cancer and neurological complications.

- **Potential Risks Associated with the OCS Liver System:**

  Subjects have the risk of not receiving organs preserved with the OCS Liver System under certain conditions including: (1) the OCS Liver System may not function properly, or there may not be personnel available trained in the use of the OCS Liver System or (2) the OCS Liver System may malfunction, or the medical staff may make an error which could lead to damage of the donor liver. If this occurs, the subject will have to wait for a new donor liver to become available. In no case does the recipient lose their place on the waiting list.

  As with any medical device, there is always a risk of extremely rare or previously unknown side effects developing from the treatment. However, at this time, there are no known potential risks other than those associated with liver transplant procedures performed under the current standard of care.

- **Potential Risk of Using a Donor Liver that is Unsuitable for Transplantation:**

  Regardless of the preservation system that is used, there is the risk that a patient can receive a liver that does not adequately function. There is the possibility that the donor liver may not meet transplantability criteria after OCS preservation and would be turned down for transplant. The anticipated frequency of this event is known. There is a risk that the surgeon may transplant a liver that does not function or functions poorly after transplant. This risk exists for any liver preservation technology.

11.2. Manner in Which the Risks Will be Minimized

The Sponsor has relied upon a number of different means, including the device design, risk analysis and management process, preclinical testing, prior clinical testing and the clinical protocol itself, to minimize the risks to subjects and to protect their safety and welfare.

The OCS Liver System has undergone extensive preclinical and animal studies to demonstrate that the device performs as intended and all material are biocompatible. Previous clinical studies, including the Liver PROTECT study, have demonstrated the safety of the device.

In addition, this clinical protocol incorporates several procedures to minimize the risks to subjects and to ensure the benefits of the clinical trial outweigh its potential risks.

- The donor liver acceptance criteria after OCS Liver System perfusion and assessment are based on clinically relevant markers for perfusion of donor livers on OCS and clinical standards of accepting conventional donor livers for transplantation. Thus, the donor liver will be fully assessed based on the current standards of evaluating donor livers before acceptance for transplantation.
- As with any liver transplant procedure, subjects will be monitored before, during and after the operative procedure. The investigators have extensive experience with liver transplants and will be trained (or have already been trained) on the use the OCS Liver System to further minimize risk.
- The trial will be monitored to ensure the identification, documentation, and analysis of adverse events; and to ensure compliance with the protocol and procedures that are in place for conducting research to protect the safety and well-being of all subjects.

Lastly, the OCS Liver PROTECT study has not raised any questions regarding safety of the device, and no safety issues or concerns have been raised by the study's independent DSMB.

11.2.1. Potential Benefits

The low utilization of donor livers has contributed to the severe shortage of donor livers. The OPTN/SRTR Annual Report indicates that, 12 months after listing, 18% of patients will die or become delisted (Kim, et al., 2019).

The OCS Liver System's preservation and assessment capabilities could potentially increase the rate of utilization of donor livers and reduce waiting list time and mortality. In addition, the OCS Liver System's ability to assess donor livers allows for the assessment of the function of the donor liver before it is transplanted.

11.2.2. Risk: Benefit Ratio

Based on the above, the benefits of using OCS Liver System technology to preserve and assess livers to ensure their suitability for liver transplantation outweigh the potential risks to trial subjects.

12. DEVICE/SITE MANAGEMENT

12.1. Packaging and Labeling

The OCS Liver Perfusion Set and accessories 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. The labeling provides instructions for use for the device. A copy of the Instructions for Use (IFU) will be provided to each investigational site.

12.2. 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 in detail in the IFU.

12.3. 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 ensure that the investigational device will not be dispensed to any person who is not a subject under the terms and conditions set forth in this protocol.

12.4. Device Complaints and Malfunctions

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

13. REGULATORY / ETHICS

This clinical trial will be conducted in accordance with the requirements of the FDA Investigational Device Exemptions regulation (21 CFR Parts 50, 56, 812, and 45 CFR part 46), and in accordance with good clinical practices.

13.1. Institutional Review Boards (IRB)

In accordance with the conditions imposed by the reviewing Institutional Review Board (IRB) to applicable regulations from Federal agency (i.e. U.S. Food and Drug Administration (FDA), with local regulations, prior to initiation of any trial procedures, the protocol, informed consent template and device labeling (if requested) will be submitted to each site's IRB for review and approval. In addition, any amendments to the protocol or informed consent form will be reviewed and approved (if necessary) by the IRB. The Sponsor must receive a letter documenting the IRB's approval at the clinical site prior to the initiation of the trial at that particular site.

13.2. Informed Consent

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) for the site. The investigator agrees to also obtain approval from the Sponsor and IRB for any written informed consent form used in the trial.

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

14. DATA COLLECTION/RECORDS/REPORTS

14.1. Investigator Records

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

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

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

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

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

14.2. Investigator Reports

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

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

14.3. Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Examples of source documents include progress notes, electronic data, computer printouts, screening logs, and recorded data from automated instruments. All data entered into the trial database must have a corresponding source document. All source documents pertaining to this trial will be maintained by the investigators and made available for inspection by authorized persons. The Sponsor may request copies of select redacted source documents.

14.4. Archiving of Records

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

15. CLINICAL MONITORING

15.1. Monitoring

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

15.2. Pre-Trial Monitoring Procedures

15.2.1. Selection of Monitors

All monitors will be qualified by education, training, and experience. Importantly, all monitors will be trained on this protocol and critical data elements prior to conducting site monitoring visits.

15.2.2. Study Initiation Visit (SIV)

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

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

15.3. Interim Monitoring Visits

Interim monitoring visits will be conducted periodically by TransMedics after scheduling a mutually convenient date with the site. The monitor will visit each site as needed to ensure the following:

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

15.4. Frequency of Monitoring Visits

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

15.5. Close-out Visit

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

- Ensure that all electronic forms have been completed.
- Ensure that any database queries have been resolved.
- Remind the investigator of the obligation to retain study records and any other post-study obligations.

15.6. Additional Auditing

Regulatory authorities 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.

15.7. 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 as soon as possible, but no later than 5 working days after the emergency occurred.

In the event of a deviations from the protocol due to an accident or mistake (e.g., protocol-mandated assessment not performed or done out of window), the site will document the deviation on the Protocol Deviation eCRF. All efforts should be made to keep protocol deviations to a minimum.

15.8. Clinical Events Committee

The Sponsor will utilize an independent Clinical Events Committee (CEC). Responsibilities of the CEC and frequency/scheduling of CEC meetings will be performed as outlined in the CEC charter.

15.9. Data Safety Monitoring Board

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 effectiveness and safety endpoints. The DSMB will make recommendations to the Sponsor regarding continuation, modification or termination of the clinical trial. Further details on member responsibilities and frequency/scheduling of DSMB meetings are contained in the DSMB charter.

15.10. Investigator Device Training

Device training will be provided to all new team members at an investigational site who have no experience with the OCS Liver System operation, prior to patient enrollment in the trial. Device training, when necessary, will be conducted at the TransMedics clinical training facility or equivalent training facility.

15.11. 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 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 unique subject numbers on the case report forms.

15.12. Amendment Policy

The investigator will not make any changes to this protocol without prior written consent from the Sponsor and subsequent approval by the IRB, except if the deviation from the protocol is necessary to protect the life and physical well-being of a subject in an emergency

16. REFERENCES

1. Kim, et al., OPTN/SRTR 2017 Annual Data Report: Liver. *Scientific Registry of Transplant Recipients*; 2019.
2. Olthoff, et al. Validation of a Current Definition of Early Allograft Dysfunction in Liver Transplant Recipients and Analysis of Risk factors. *Liver Transplantation* 16(8):943-949, 2010.
3. Pan, et al. Cold Ischemia Time Is an Important Risk Factor for Post-Liver Transplant Prolonged Length of Stay. *Liver Transplantation*, Vol. 24, No. 6, 2018.
4. Vogel, et al. The Role of Normothermic Extracorporeal Perfusion in Minimizing Ischemia Reperfusion Injury. *Transplantation Reviews* 26 (2012) 156-162.
5. Wertheim, et al. major Challenges Limiting Liver Transplantation in the United States. *Am J Transplant.* 2011 September; 11 (9): 1773-1784.
6. Zhai, et al. Ischemia-Reperfusion Injury in Liver Transplantation-From Bench to Bedside. *Nat Rev Gastroenterol Hepatol.* 2013 February; 10 (2): 79-89.

APPENDIX 1. LIVER TISSUE BIOPSY, BILE DUCT SPECIMEN, & SCORING PROTOCOL

Liver Parenchyma Tissue Sample:

- Each tissue specimen is a 2.0 cm long 16-gauge needle biopsy taken perpendicular to the liver capsule from the right lobe. It should be stressed that the needle NOT be inserted parallel to the capsule.
- The tissue sample can then be placed in 10% neutral-buffered formalin, which is standard at most institutions.
- The specimen container must be CLEARLY LABELED with an anonymous code and specimen information. Bar coding is preferable.
- The label should also contain the timing of the biopsy: a) donor pre-retrieval; b) post-preservation (before implant); and c) post-reperfusion.

Timing of Liver Biopsy Samples:

- Liver tissue samples taken at the following timepoints:
  - Donor liver pre-retrieval. Only donor livers that are clinically suspected to be fatty by retrieval team visualization, will require a pre-retrieval biopsy readout to estimate the degree of macrosteatosis and confirm eligibility (≤40% macrosteatosis)
  - Post-OCS preservation at the end of back preparation and immediately before the start of re-implantation
  - 90-120 minutes after reperfusion of the transplanted liver (prior to abdominal closure).

Bile Duct Specimens (if applicable):

- Any tissue trimmed from the bile duct or cystic duct should be placed into 10% neutral buffered formalin, as above, and CLEARLY LABELED, as to the center and participant and location of the sample. For example, 001-001 "distal common bile duct trimming."

Timing of Bile Duct Specimen:

- Pathology sample of common bile duct taken post-preservation:
  - Post preservation at the end of back preparation and immediately before the start of re-implantation OR
  - Post reperfusion-Prior to biliary anastomosis.

Refer to core lab collection manual in the PROTECT Study Manual

Score

PARENCHYMAL CHANGES:

Total biopsy length:_____ mm Total number of portal tracts: _____ Biopsy Adequate: Yes No

Overall architectural integrity: normal/intact mild moderate severe distortion

1. Lobular necrosis:
   - 1.1 Overall severity: ( ) NONE ( ) MILD ( ) MOD ( ) SEV ( ) N/A
   - 1.2 Primary location: ( ) Periportal ( ) Midzonal ( ) Perivenular ( ) Panlobular ( ) NA
   - 1.3 Secondary location ( ) Periportal ( ) Midzonal ( ) Perivenular ( ) Panlobular ( ) NA
   - 1.4 Tertiary location: ( ) Periportal ( ) Midzonal ( ) Perivenular ( ) Panlobular ( ) NA
2. Lobular inflammation:
   - 2.1 Overall severity: ( ) NONE ( ) MILD ( ) MOD ( ) SEV ( ) N/A
   - 2.2 Primary location: ( ) Periportal ( ) Midzonal ( ) Perivenular ( ) Panlobular ( ) NA
   - 2.3 Secondary location: ( ) Periportal ( ) Midzonal ( ) Perivenular ( ) Panlobular ( ) NA
3. Lobular inflammation type:
   - 3.1 Primary type: ( ) Neutrophils ( ) Eosinophils ( ) Macrophage/monocyte ( ) Lymphocytes ( ) Plasma cells
   - 3.2 Secondary type: ( ) Neutrophils ( ) Eosinophils ( ) Macrophage/monocyte ( ) Lymphocytes ( ) Plasma cells
   - 3.3 Tertiary type: ( ) Neutrophils ( ) Eosinophils ( ) Macrophages/monocytes ( ) Lymphocytes ( ) Plasma cells
4. Lobular Steatosis:
   - 4.1 Overall severity: ( ) NONE ( ) MILD ( ) MOD ( ) SEV ( ) N/A
   - 4.2 Predominant distribution: ( ) Periportal ( )Midzonal ( ) Perivenular ( ) Panlobular ( ) NA
5. Liver Sinusoidal Endothelial Cell (LSEC) integrity/coverage (based on CD31 staining)
   - 5.1 Overall percentage of sinusoids covered _____ (nearest 10%)
   - 5.2 Primary LSEC loss: ( ) Periportal ( )Midzonal ( ) Perivenular ( ) Panlobular ( ) NA
   - 5.3 Secondary LSEC loss: ( ) Periportal ( )Midzonal ( ) Perivenular ( ) Panlobular ( ) NA

EXTRA-HEPATIC BILE DUCT CHANGES:

(adapted from Hansen et al. Virchows Arch 2012;461:41-48; and op den Dries 37T43TJ Hepatol37T43T. 2014 Jun;60(6):1172-9):

1. Surface epithelial loss: ( ) 0: no loss ( ) 1: ≤ 50% ( ) > 50%
2. Bleeding: ( ) 0: no bleeding ( ) 1: ≤ 50% ( ) > 50%
3. Thrombi: ( ) 0: no thrombi ( ) 1: thrombi present
4. Vascular lesions: ( ) 0: no lesions ( ) 1: ≤ 50% vessels ( ) > 50% vessels
5. Arteriolonecrosis: ( ) 0: no lesions ( ) 1: ≤ 50% vessels ( ) > 50% vessels
6. Duct necrosis: ( ) 0: no lesions ( ) 1: <25% ( ) 2: 25-50% ( ) 3: 50-75% ( ) > 75% necrosis
7. Inflammation: ( ) 0: none; ( ) 1: at least > 10 leukocytes/HPF; ( ) 2: >50/HPF
8. Subluminal gland injury: ( ) 0: no injury ( ) 1: ≤ 50% ( ) > 50%
9. Deep gland injury: ( ) 0: no loss ( ) 1: ≤ 50% ( ) > 50%

APPENDIX 2. SCHEDULE OF CLINICAL ASSESSMENTS

Evaluations	
Eligibility & ID	X
Demographics/Characteristics	X
Donor Cause of Death	X
Donor Medical & Social History	X
Donor Liver Assessment	X
Donor Cross Clamp Time and Flush Detail	X
Post-Preservation Liver Biopsy and if applicable Bile duct specimen	X
OCS Preservation Parameters	X
OCS Liver Enzymes & Lactate Levels	X
Device Malfunction (if applicable)	X
Non-transplant Reasons (if applicable)	X

Evaluations	Recipient Schedule of Assessments					
	Tx. Day - Day 7 Post-Tx.	Discharge	Day 30	Month 6	Month 12	Month 24
Eligibility & Informed Consent	X					
Demographic/Characteristics	X					
Medical & Risk Factors	X					
Transplant Details	X					
Early Liver Allograft Dysfunction (EAD) Surveillance	X					
Mechanical Ventilator Support	X					
Patient Survival	X	X	X	X	X	X
Graft Survival	X	X	X	X	X	X
Immunosuppressive Meds & Induction (if applicable)	X	X				
Initial ICU & Hospital Stay	X	X				
Liver graft-related (AE's & SAE's)	X	X	X	X		
Liver graft-related re-hospitalizations				X	X	
Ischemic biliary complications				X	X	
Liver Biopsy *	X				X	X
* ONLY tests regularly scheduled per center standard of care or performed due to a clinical cause at these timepoints will be collected.						