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Clinical Protocol and Investigational Plan

Prospective Trial to Evaluate the Effectiveness of The Portable Organ Care System (OCS™) Liver for Preserving, Optimizing and Assessing Currently Seldom Utilized DCD Donor Livers for Transplantation (OCS™ Liver DCD Trial)

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OCS™ LIVER DCD TRIAL SYNOPSIS

Protocol Title	Prospective Trial to Evaluate the Effectiveness of The Portable Organ Care System (OCS™) Liver for Preserving, Optimizing and Assessing Currently Seldom Utilized DCD Donor Livers for Transplantation (OCS™ Liver DCD Trial)
Objectives	To evaluate the safety and effectiveness of the OCS™ Liver to preserve, optimize the condition and assess livers from DCD donors that currently are seldom used for liver transplants due to limitations of cold static storage with extended warm ischemic time and older donors.
Trial Design	Prospective, pivotal, single-arm
Trial Size	A maximum of 25 participating sites to enroll 130 transplanted liver recipients from DCD donors
Donor Liver Eligibility Criteria	**Inclusion** • Maastricht Category III DCD donor, defined as expected death after the withdrawal of life-supportive therapy (WLST); **AND** • Donor age 18-55 years and warm ischemic time (WIT) > 30 and ≤ 120 minutes, with WIT defined as time from withdrawal of life support to donor liver flush in the donor. The final clinical decision whether to accept or reject a donor liver prior to initiation of the OCS Liver perfusion, will be according to an individual transplant center's internal clinical cut-off for the upper limit for warm ischemic time (but not to exceed 120 minutes); **OR** • Donor age > 55 years and with WIT ≤ 120 minutes, with WIT defined as time from withdrawal of life support to donor liver flush in the donor. The final clinical decision whether to accept or reject a donor liver prior to initiation of the OCS Liver perfusion, will be according to an individual transplant center's internal clinical cut-off for the upper limit for warm ischemic time (but not to exceed 120 minutes). **Exclusion** • Presence of moderate or severe traumatic liver injury and livers with active bleeding (e.g., hematomas, laceration) • HIV and/or Hepatitis B surface antigen positive serology • Liver intended for split transplants.
Recipient Eligibility Criteria	**Inclusion** • Registered primary liver transplant candidate • Age ≥ 18 years old • Obtained informed consent. **Exclusion** • Acute, fulminant liver failure • Prior solid organ or bone marrow transplant

	• Ventilator dependent on day of transplant/donor organ offer.
Primary Effectiveness Endpoint	Liver Graft Survival through 6 months post-transplant, as defined per UNOS data collection criteria for Graft Status after liver transplantation*. * If patient dies and the death was a result of some other factor unrelated to graft failure, the graft will be considered functioning not failed (https://unos.org/wp-content/uploads/unos/Adult_TRF_Liver.pdf)

Secondary Effectiveness and OCS Donor Liver Assessment Endpoints	• Rate of donor liver utilization after OCS Liver perfusion, defined as the number of eligible donor livers that were instrumented and perfused on OCS Liver and successfully transplanted, divided by the number of eligible donor livers that were instrumented and perfused on OCS.
	• Incidence of ischemic biliary cholangiopathy at 6 months post-transplant;
	• 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/l within the first 7 postoperative days (for hospitalized patients only)
	  ○ Bilirubin≥10 mg/dl on postoperative day 7, ± 1 day (for hospitalized patients only)
	  ○ INR ≥ 1.6 on postoperative day 7, ± 1 day (for hospitalized patients only).

Other Endpoints	The proportion of patient and graft survival at day 30 days, 6 months, 12 months, 24 months, 36 months, 48 months, and 60 months.
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 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, in the absence of immunologic or surgical causes) • Ischemic biliary complications (ischemic biliary strictures, and non-anastomotic bile duct leaks) • Vascular complications (non-surgical hepatic artery stenosis, hepatic artery thrombosis and portal vein thrombosis) • Liver graft-related coagulopathy • Liver allograft infections (liver abscess, cholangitis).
Follow-up	Patient and graft survival will be collected for up to 5 years post-transplant; including post-market follow-up.
Analysis Populations	• The Per Protocol (PP) Population will consist of all subjects who are transplanted in the study with a liver preserved on OCS and have no major protocol violations. The primary analysis of effectiveness will be based on the PP Population. • The Modified Intent-to-Treat Population (mITT) will consist of all subjects who are transplanted in the study with a liver preserved on OCS. The mITT population will be considered a sensitivity analyses of effectiveness. The safety analysis will also be based on the mITT population. • The Donor Liver (DL) Population will consist of all donor livers eligible for the study that were instrumented on the OCS.
Effectiveness Analysis	The primary effectiveness endpoint will show that the 6-month graft survival rate meets an objective performance goal (OPG) defined as 0.765 (76.5%). This OPG was determined based on the 2019 SRTR/OPTN annual data report showing that 6-month graft survival for the

	recipients of DCD livers is 88.5%, with an 12% margin to allow for the fact that extended warm ischemia times and other risk factors are allowed and expected in this study. As noted above, the UNOS statistic upon which the OPG is based does not include deaths that are unrelated to graft failure, and the primary effectiveness endpoint will be defined similarly to the UNOS national statistics. The formal statistical hypothesis test is as follows: H_0: $\pi_{OCS\ liver} \leq 0.765$, and H_1: $\pi_{OCS\ liver} > 0.765$ where $\pi_{OCS\ liver}$ is the 6-month graft survival rate for organs preserved on the OCS Liver System. The primary effectiveness endpoint will be summarized using counts and percentages and an exact 95% confidence interval for the true percentage based on the binomial distribution. The lower bound of confidence interval should be greater than 0.765 to reject the null hypothesis H_0. If any patient has missing 6-month graft survival in the end of study, the Kaplan-Meier estimates will be used to test null hypothesis. Subject not having 6-month graft survival will be censored at the date of last contact during the study. The lower limit of Kaplan-Meier estimates of 95% confidence interval at 6 months should be greater than 0.765 to reject the null hypothesis H_0. Each secondary effectiveness endpoint, except the rate of donor liver utilization after OCS perfusion, 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 rate of donor liver utilization after OCS perfusion will be summarized using counts and percentages and an exact 95% confidence interval for the true percentage based on the binomial distribution. This endpoint will be analyzed using the donor liver population.
Safety Analysis	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 will be summarized using descriptive statistics. A 95% confidence interval for the mean based on the t-distribution will be presented.
Sample Size Determination	Sample size calculations are based on the following specifications: 1. Comparison to Objective Performance Goal (OPG) 2. Endpoint is 6-month graft survival 3. One-sided, exact binomial test 4. Alpha = 0.025 5. Power = 80% 6. True proportion = 0.88 7. Objective Performance Goal = 0.765. Based on the above specifications, a sample size of 101 subjects is required. The sample size will be increased to 130 to allow for a sufficient number of subjects in the per protocol population.
Trial Sponsor	TransMedics, Inc. 200 Minuteman Road, Suite 302 Andover, MA, USA 01810

1. INTRODUCTION AND BACKGROUND

Today, liver transplantation is universally accepted as the only treatment option for end-stage liver disease, acute fulminant hepatic failure, hepatocellular carcinoma, hilar cholangiocarcinoma and several metabolic disorders. However, the availability of donor liver allografts has not kept pace with the demand. For example, in the 2019 SRTR/OPTN Annual Report, there were 13,239 candidates on the liver transplant waiting list, with only 7,630 transplants performed in that same year. These realities have led to efforts to expand the existing deceased donor pool, including the use of donors after circulatory death (DCD).

However, early experience with DCD livers was not favorable, as prolonged donor warm ischemia time (DWIT) and ischemia-reperfusion injury associated with cold storage likely played a large role in the high rate of primary non-function, hepatic artery thrombosis, ischemic cholangiopathy, and allograft failure (Jadlowiec and Taner, 2016). There have been several large retrospective analyses which have identified DCD donor-related variables associated with recipient outcomes.

Mateo, et al. (2006) performed an analysis of the UNOS database comparing recipients of DCD donors to DBD donors. The DCD group was comprised of 367 liver grafts from DCD donors over the years 1996-2003, while the control group comprised 33,111 DBD donor livers during that same time period. Overall graft survival from DCD donors were significantly inferior to those from DBD donors, with the one-year graft survival for DCD donors at 71% compared to 80% for DBD donors. In this study, the authors considered DCD donor livers with DWIT ≤ 30 minutes to be “low risk” and those with DWIT > 30 minutes to be “high risk.”

Mathur, et al. (2010) used data from the Scientific Registry of Transplant Recipients (SRTR) to investigate donor and recipient risk factors associated with inferior DCD outcomes. A retrospective cohort of 1,567 recipients of DCD liver transplants was obtained. Recipients were transplanted in the years 2001-2009. Notably, the mean donor age in this study was 35.2 ± 15.4 years, the mean cold ischemia time was 7.5 hours and the mean donor warm ischemia time (DWIT) was 16 minutes. Significant increases in graft failure were noted with: DWIT ≥ 35 minutes (HR 1.84, p=0.002), donor age 50-60 years (HR= 1.39, p=0.0047) and donor age ≥ 60 (HR 1.88, p=0.0011). This study illustrates the donor WIT distribution among the 1,567 recipients. Only 3.8% of the DCD liver transplant recipients had grafts transplanted with donor warm ischemia times greater than 35 minutes.

Eren, et al. (2016) published a review of studies to date on DCD liver transplants, including a summary table of published single center studies on outcomes of recipients of DCD livers compared to DBD livers. The majority of studies, published from 2003-2005 had mean donor age less than 40 years and donor WIT less than 25 minutes. The majority of studies showed that donor age > 50 years and DWIT > 30 minutes are risk factors for graft failure associated with DCD liver transplants.

1.1. Current Status of DCD Liver Transplants in the U.S.

The 2019 OPTN/SRTR Annual report demonstrates that DCD liver transplants are rarely performed in the U.S. (Kim, et al., 2019). Of the 7483 liver transplants in 2017, only 514 (6.9%) were from DCD donors. Furthermore, there is a large pool of unutilized DCD donors. In 2017, the percentage of livers not transplanted out of all DCD donors was 30%, compared to 9% for

DBD donors. The most recent report provides the nationwide average graft survival for all recipients of DCD liver transplants. As shown in Figure 1 below, at six months post-transplant, graft survival for DCD livers was 88.5%, compared to 91.5% for DBD recipients.

Figure 1: Graft survival for DCD and DBD liver grafts through 5 years post-transplant from OPTN national data (Figure LI 66 from Kim, et al., 2019)

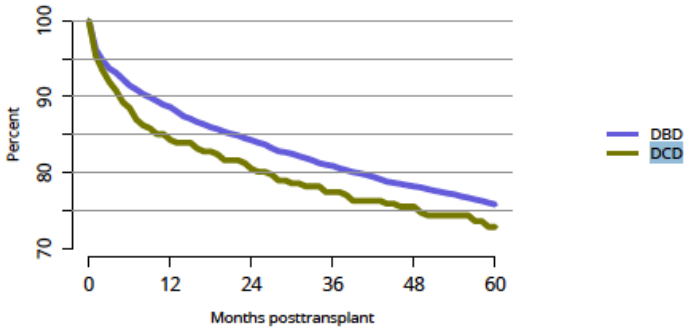

Figure LI 66. Graft survival among adult deceased donor liver transplant recipients, 2012, by DCD status. Graft survival estimated using unadjusted Kaplan-Meier methods. DCD, donation after circulatory death; DBD, donation after brain death.

However, it must be emphasized that the national averages reflect standard of care DCD liver transplants in which WIT < 30 minutes and donor age and other risk factors are very carefully managed. There is an unmet need for new technologies that can expand the donor pool and allow improved utilization of DCD livers with acceptable clinical outcomes to balance the growing demand for liver transplantation and lack of viable therapies for these patients with end-stage liver disease. The purpose of this study is to explore the use of the OCS Liver System to preserve, optimize the condition and assess DCD livers that are currently not utilized for liver transplantation in the U.S. today. If successful, this study will demonstrate that the OCS Liver System can be used to expand the donor pool and allow more life-saving liver transplants to be available for patients on the waiting list.

2. REPORTS OF PRIOR 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 were also provided in the OCS Liver PROTECT Trial G140192 that demonstrated the safety, suitability, and performance of the OCS Liver System for preservation of donor livers.

The design of the OCS Liver System for the subject IDE is identical to that being studied under G140192. The change in indication does not impact the applicability of the nonclinical information previously submitted to G140192. Accordingly, new nonclinical information is not warranted to support initiation of the subject IDE.

2.2. OCS Liver PROTECT Trial (G140192)

The PROTECT Study is a prospective, pivotal, randomized study of the OCS Liver being conducted in the United States. 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 static cold storage. T he 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 safety and effectiveness of the OCS™ Liver to preserve, optimize the condition and assess livers from DCD donors that currently are seldom used for liver transplants due to limitations of cold static storage with extended warm ischemic time and older donors.

4.1. Type of the Trial

A prospective, multi-center, single-arm controlled pivotal trial.

4.2. Trial Size and Subject Follow-up

This trial will be conducted at up to 25 institutions in the United States and will include up to 130 transplanted liver recipients from DCD donors. All subjects will be followed for 5 years post-transplant.

4.3. Trial Endpoints

4.3.1. Primary Effectiveness Endpoint

Liver graft survival through 6 months post-transplant, as defined per UNOS data collection criteria for graft status after liver transplantation*.

* If patient dies and the death was a result of some other factor unrelated to graft failure, the graft will be considered functioning not failed (see https://unos.org/wp-content/uploads/unos/Adult_TRF_Liver.pdf).

4.3.2. Secondary Effectiveness Endpoints

- Rate of donor liver utilization after OCS Liver perfusion, defined as the number of eligible donor liver that were instrumented and perfused on OCS Liver and successfully transplanted, divided by the number of eligible donor livers that were instrumented and perfused on OCS.
- Incidence of ischemic biliary cholangiopathy at 6 months post-transplant.
- 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/l within the first 7 postoperative days (Day 7 for hospitalized patients only)
    - Bilirubin≥10 mg/dl on postoperative day 7, ± 1 day (Day 7 for hospitalized patients only)
    - INR ≥ 1.6 on postoperative day 7, ± 1 day (Day 7 for hospitalized patients only).

4.3.3. Other Endpoints

- The proportion of patient and graft survival at Day 30, 6 months, 12 months, 24 months, 36 months, 48 months, and 60 months.

4.3.4. Safety Endpoint

Safety will be analyzed 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 liver graft-related serious adverse events through the 30 days post-liver transplant (per subject, consisting of the following events; at most one per type per person):

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

5. TRIAL POPULATION

Patients with end-stage liver disease requiring liver transplantation.

5.1. Donor Eligibility Criteria

5.1.1. Donor Inclusion Criteria

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

AND

- Donor age 18-55 years and warm ischemic time (WIT) > 30 and ≤ 120 minutes, with WIT defined as time from withdrawal of life support to donor liver flush in the donor.

  The final clinical decision whether to accept or reject a donor liver prior to initiation of the OCS Liver perfusion, will be according to an individual transplant center's internal clinical cut-off for the upper limit for warm ischemic time (but not to exceed 120 minutes);

OR

- Donor age > 55 years and with WIT ≤ 120 minutes, with WIT defined as time from withdrawal of life support to donor liver flush in the donor.

  The final clinical decision whether to accept or reject a donor liver prior to initiation of the OCS Liver perfusion, will be according to an individual transplant center's internal clinical cut-off for the upper limit for warm ischemic time (but not to exceed 120 minutes).

5.1.2. Donor Exclusion Criteria

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

- Presence of moderate or severe traumatic liver injury and livers with active bleeding (e.g., hematomas, laceration)
- HIV and/or Hepatitis B surface antigen positive serology
- Liver intended for split transplants.

5.2. Recipient Eligibility Criteria

5.2.1. Recipient Inclusion Criteria

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

- Registered primary liver transplant candidate
- Age ≥ 18 years old
- Obtained informed consent.

5.2.2. 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
- Ventilator dependent on day of transplant/donor organ offer.

5.3. Screening Procedures

5.3.1. Recipient – Screening and Enrollment

Recipients will be screened for potential eligibility for the trial. Those patients who initially appear eligible will have the trial thoroughly explained to them and will be asked for consent for participation.

A recipient will be considered enrolled in the trial only when a matching DCD liver is identified, procured, preserved on OCS and transplanted into a consented eligible recipient. Data will be collected according to the Schedule of Assessments found in Appendix 1.

5.3.2. Donor Liver – Initial Screening, Retrieval and OCS Preservation

The retrieval team will evaluate the donor and the quality and suitability of the liver for transplantation in general and for inclusion in the trial. After final evaluation of the donor liver in the donor's abdomen and upon acceptance into the trial, the investigators will retrieve and preserve the donor liver using the OCS Liver System according to the Instructions for Use.

Data collected that relates to organ retrieval, OCS preservation and assessment will be collected according to the Schedule of Assessments in Appendix 1.

5.3.3. Donor Liver Assessment on OCS Liver System and Acceptance for Transplantation

All donor livers that are preserved on OCS Liver System MUST meet all three conditions of the following clinical criteria to be eligible for transplantation into a recipient:

- DCD Donor livers on OCS Liver System are deemed to be clinically acceptable for transplantation by the Site Principal Investigator based on their clinical judgment and interpretation of OCS Liver System's hemodynamic and metabolic parameters;
- OCS Liver System perfusate lactate levels that are trending down on OCS Liver System from initial sample to final sample taken during OCS Liver perfusion and below 10 mmol/l at the end of OCS perfusion;
- Able to achieve and maintain OCS Liver System perfusion parameters for the organ; mean Hepatic Artery Pressures (HAP), Hepatic Artery Flows (HAF) , mean Portal Vein Pressure (PVP) and Portal Vein Flow (PVF) as recommended in the IFU.

Any decision to turn down livers after they have been retrieved, preserved and assessed on OCS™ Liver System should be made by the Site Principal Investigator (or should be made in consultation with the site Principal Investigator), and the clinical reason for turning down the donor liver for transplantation will be documented.

5.4. Enrolled DCD Donor Livers and Recipients

- Recipient Enrollment: for the assessment of post-transplant outcomes, a consented potential recipient will be considered enrolled in the trial when they are transplanted with any DCD donor liver preserved and assessed on OCS Liver System.
- DCD Donor Liver Enrollment: for the assessment of donor liver utilization rate, a DCD donor liver will be considered enrolled in the trial if it meets the eligibility criteria for donor liver inclusion and was instrumented on the OCS Liver System for ex-vivo perfusion and assessment.

6. DATA COLLECTION AND FOLLOW-UP

Data collection will include:

Donor:

- Eligibility information
- Demographics, Medical and Social Histories, Cause of Death
- Liver assessment including warm ischemic time, cross clamp and flush times
- OCS preservation parameters
- OCS liver enzymes and lactate levels
- Device malfunction (if applicable)
- Non-transplant reason(s) (if applicable).

Recipient:

- Eligibility information
- Demographics, Medical History and risk factors
- Transplant details, including documentation of reconstruction of any accessory vessels or anatomical abnormalities prior to perfusion
- Lab assessments:
    - AST – from ICU admission through Day 7 ± 1 day (for hospitalized patients only)
    - Bilirubin – Day 7 ± 1 day (for hospitalized patients only)
    - INR – Day 7 ± 1 day (for hospitalized patients only)
- Subject and graft survival from Day 30 through Month 60. Follow-up at these timepoints may be done via telephone and/or review of the subject's medical record.
- Presence/absence of ischemic cholangiopathy at 6 months
- Liver graft-related serious adverse events up to 30 days post-transplant
- Serious adverse events up to 30 days post-transplant
- Protocol deviations (if applicable).

See the Schedule of Assessments in Appendix 1 for details and time windows for data collection parameters.

7. EVALUATION OF ADVERSE EVENTS

In this trial, only liver graft-related serious adverse events (LGRSAEs) as defined in Section 7.1 below and serious adverse events (SAEs) will be collected through Day 30 post-transplant.

7.1. Evaluation of Liver Graft-Related Serious Adverse Events

Liver Graft-Related Serious Adverse Events are those which have any untoward effect on the health or safety of the patient and that are related to the transplanted liver (except for acute rejection). LGRSAEs 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 and will consist only of the following events:

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

All LGRSAEs will be followed until resolution or stabilization of the event.

7.2. 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.

7.3. Anticipated Adverse Events

Anticipated adverse events that are related to liver transplantation (and not specific to the OCS device) 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
- Hyperammonemia
- 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.

7.4. Unanticipated Adverse Device Effect (UADE)

An UADE is 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.

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

7.5. Recording and Reporting of Adverse Event

All LGRSAEs and SAEs will be collected through 30 days post-transplant and should be entered as soon as possible into the study database. For all LGRSAEs and SAEs, the investigator may be asked to supply any additional source documents that may be deemed necessary by the Sponsor.

7.5.1. Relationship of an LGRSAE or SAE to OCS Liver

The investigator will assess the relationship of the event to the OCS method 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™ Liver 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 the adverse event.
- ***Unlikely Related:*** There is a temporal relationship with preservation with the OCS™ Liver 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 and the adverse event.

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.

7.6. Pre-Existing Conditions

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

8. STATISTICAL METHODS

8.1. 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 percentage.

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

8.2. Analysis Populations

Data analysis and summarization will be performed using the analysis populations defined below.

8.2.1. Per Protocol Population

The Per Protocol (PP) population will consist of all subjects who are transplanted in the study with a liver preserved on OCS Liver System and have no major protocol deviations. The PP population will be used for primary analysis of effectiveness.

8.2.2. Modified Intent-to-Treat Population

The modified Intent-to-Treat (mITT) population will include subjects are who transplanted in the study with a liver preserved on OCS Liver System. The mITT population will be used for the sensitivity analysis of effectiveness. The safety analysis will also be based on the mITT population.

8.2.3. Donor Liver Population

The Donor Liver Population will consist of all donor livers eligible for the study that were instrumented on the OCS. The Donor Liver Population will be used for rate of donor liver utilization after OCS Liver perfusion.

8.3. Data Analysis

The statistical analysis plan (SAP) provides 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.

8.3.1. 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).

8.3.2. 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.

8.3.3. 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.

8.3.4. Effectiveness Analysis

8.3.4.1. Primary Endpoint

The primary endpoint for this study is Liver Graft Survival through 6 months post-transplant, as defined per UNOS data collection criteria for Graft Status after liver transplantation*.

> * If patient dies and the death was a result of some other factor unrelated to graft failure, the graft will be considered functioning not failed (https://unos.org/wp-content/uploads/unos/Adult_TRF_Liver.pdf.

The primary effectiveness endpoint will show that the 6-month graft survival rate meets a performance goal defined as 0.765 (76.5%). This OPG was determined based on the 2019 SRTR/OPTN annual data report showing that 6-month graft survival for the recipients of DCD livers is 88.5%, with an 12% margin to allow for the fact that extended warm ischemia times and other risk factors are allowed and expected in this study. As noted above, the UNOS statistic upon which the OPG is based does not include deaths that are unrelated to graft failure, and the primary effectiveness endpoint will be defined similarly to the UNOS national statistics.

The formal statistical hypothesis test is as follows:

$$H_0: \pi_{OCS\ liver} \leq 0.765, \text{ and}$$
$$H_1: \pi_{OCS\ liver} > 0.765$$

where $\pi_{OCS\ liver}$ is the 6-month graft survival rate for organs preserved on the OCS Liver System.

The primary effectiveness endpoint will be summarized using counts and percentages and an exact 95% confidence interval for the true percentage based on the binomial distribution. The lower limit of confidence interval should be greater than 0.765 to reject the null hypothesis H_0.

If any patient has missing 6-month graft survival in the end of study, the Kaplan-Meier estimates will be used to test null hypothesis. Subject not having 6-month graft survival will be censored at the date of last contact during the study. The lower limit of Kaplan-Meier estimates of 95% confidence interval at 6 months should be greater than 0.765 to reject the null hypothesis H_0. Tipping point analysis will be provided for sensitivity analysis (Section 8.5).

8.3.4.2. Secondary Endpoints

Each secondary effectiveness endpoint will be summarized using counts and percentages and an exact 95% confidence interval for the true percentage based on the binomial distribution. The secondary effectiveness endpoints, except the rate of donor liver utilization, will be analyzed using the PP population as primary analysis and using the mITT population as sensitivity analysis.

8.3.4.3. Other Endpoints

The proportion of patient and graft survival at day 30, 6 months, 12 months, 24 months, 36 months, 48 months and 60 months will be calculated with 95% confidence interval.

The other endpoints will be analyzed with both PP population and mITT population.

8.4. Safety Analysis

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

8.5. Treatment of Missing Data

A tipping point analysis of the primary endpoint will be performed in the following manner for the PP population and mITT population. Initially the analysis will be performed with all missing values for the primary endpoint defined to be successes (i.e., not graft failures). If this analysis results in rejection of the null hypothesis, the analysis will continue by setting one missing value to be a graft failure and all of the other missing values to be successes. This procedure will continue in the same manner, each time setting one additional missing value to be a failure, until the first time that the analysis does not result in rejection of the null hypothesis. This point is referred to as the tipping point, the point at which conclusions change from being favorable to the treatment to being unfavorable.

No other data imputation is planned for effectiveness and safety measures.

8.6. Sample Size Determination

Sample size calculations are based on the following specifications:

- Comparison to Objective Performance Goal (OPG)
- Endpoint is 6-month graft survival
- One-sided, exact binomial confidence interval
- Alpha = 0.025
- Power = 80%
- True proportion = 0.88
- Objective Performance Goal = 0.765.

Based on the above specifications, a sample size of 101 transplanted subjects with DCD donor liver preserved on OCS Liver System is required. The sample size will be increased to 130 to allow for a sufficient number of subjects in the per protocol population.

8.7. Stopping Rule

The following stopping rules are to be used in the study:

1. Stop the study if and when there are 4 deaths before Day 30 or initial hospital discharge post-transplant (whichever is later) among the first 10 recipients; or
2. Stop the study if and when there are 4 incidences of primary non-function within the first 7 days post-transplant among the first 10 recipients; or
3. Stop the study if and when there are 7 deaths before Day 30 or initial hospital discharge post-transplant (whichever is later) among the first 20 recipients; or
4. Stop the study if and when there are 7 incidences of primary non-function within the first 7 days post-transplant among the first 20 recipients.

This rule is based on the following: Let p denote the true proportion of recipients transplanted with an OCS-preserved liver for whom the recipient does not survive until Day 30 or initial hospital discharge post-transplant (whichever is later) or let p denote the true proportion of recipients transplanted with an OCS-preserved liver for whom the recipient experiences primary non-function of the graft within the first 7 days post-transplant. Stop the study (based on 10 or 20 recipients) if there is statistical evidence that the true value of p exceeds 0.12, i.e., if the exact 97.5% lower confidence bound for p exceeds 0.12 (12%). The above statistical stopping rules would be applied to all combinations of number of deaths and incidences of PNF and number of recipients that were observed in the study.

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.

9. 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.

9.1. 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. However, since this study includes donor livers currently seldom utilized for transplantation, the potential additional chance for a liver is an added benefit. 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. This trial is designed to utilize livers that are seldom accepted for transplantation using cold storage preservation. 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.

9.2. 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 and studies of the OCS Liver System outside the U.S., 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, this will be the second IDE trial involving the OCS Liver System. The first study, the OCS Liver PROTECT study (G140192) has not raised any questions regarding safety of the device.

9.2.1. Potential Benefits

The low utilization of donor livers from DCD donors has contributed to the severe shortage of donor livers. The OPTN/SRTR Annual Report indicates that, 12 months after listing, 21% of patients will die or become delisted and only 42% of subjects listed will receive a transplant (Kim, et al., 2019).

The OCS Liver System's preservation and assessment capabilities could potentially increase the rate of utilization of DCD donor livers that are seldom used due to the limitations of cold storage techniques. Utilization of these donor livers could improve the chances of waiting list recipients to receive a lifesaving liver transplant 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.

9.2.2. Risk: Benefit Ratio

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

10. DEVICE/SITE MANAGEMENT

10.1. 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.

10.2. 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.

10.3. 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.

10.4. 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.

11. 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.

11.1. 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.

11.2. 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.

12. DATA COLLECTION/RECORDS/REPORTS

12.1. 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.

12.2. 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.

12.3. 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.

12.4. 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.

13. CLINICAL MONITORING

13.1. 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.

13.2. Pre-Trial Monitoring Procedures

13.2.1. 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.

13.2.2. 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.

13.3. 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.

13.4. 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.

13.5. 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.

13.6. 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.

13.7. 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.

13.8. 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.

13.9. 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.

13.10. Investigator Device Training

Device training will be provided to all new investigators and support staff that have no experience with the OCS Liver device 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.

13.11. 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.

13.12. 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.

14. REFERENCES

1. Eren, et al. Donations After Circulatory Death in Liver Transplant. *Exp Clin Transplant*; 2016 October; 14(5); 463-470.
2. Israni, et al. OPTN/SRTR 2017 Annual Data Report: Deceased Organ Donation. Scientific Registry of Transplant Recipients; 2019.
3. Jadlowiec and Taner. Liver transplantation: Current status and challenges. World J Gastroenterol; 2016 May 14; 22(18): 4438-4445.

4. Kim, et al., OPTN/SRTR 2017 Annual Data Report: Liver. Scientific Registry of Transplant Recipients; 2019.
5. Mateo, et al. Risk Factors for Graft Survival After Liver Transplantation from Donation After Cardiac Death Donors: An Analysis of OPTN/UNOS Data. American Journal of Transplantation; 2006; 6: 791–796.
6. Mathur, et al. Donation after Cardiac Death Liver Transplantation: Predictors of Outcome. American *Journal of Transplantation;* 2010; 10: 2512–2519.

APPENDIX 1. SCHEDULE OF CLINICAL ASSESSMENTS

Donor Data Collection Overview	
Eligibility & ID	X
Demographics/Characteristics	X
Donor Cause of Death	X
Donor Medical & Social History	X
Warm Ischemic Time	X
Donor Liver Assessment	X
Donor Cross Clamp Time and Flush Detail	X
OCS Preservation Parameters	X
OCS Liver Enzymes & Lactate Levels	X
Device Malfunction (if applicable)	X
Non-transplant Reason(s) (if applicable)	X

	Recipients Data Collection Overview									
	Day 0[1]	**Day 1-6[2]**	**Day 7**	**Day 30 ± 7 days**	**Month 6 ± 1**	**Month 12 ± 1**	**Month 24 ± 2**	**Month 36 ± 2**	**Month 48 ± 2**	**Month 60 ± 2**
Informed Consent	X									
Eligibility	X									
Demographics and Medical Hx	X									
Tx Details	X									
AST	X	X[3]	X[3]							
Bilirubin			X[3]							
INR			X[3]							
Patient survival				X	X	X	X	X	X	X
Graft survival				X	X	X	X	X	X	X
Ischemic cholangiopathy surveillance					X					
LGRSAEs	X	X	X	X						
SAEs	X	X	X	X						
ICU Stay	X	X	X	X						
Initial Hospital Admission	X	X	X	X						

[1] Day 0 is defined as date of transplant and ICU admission immediately post-liver transplantation.
[2] Day 1 starts 24 hours after ICU admission date and time.
[3] Only if subject is still hospitalized post-transplant. All discharged patients will not be required to have these labs collected.