ORGAN RECOVERY SYSTEMS

CLINICAL RESEARCH PROTOCOL

A Prospective Randomized Multi-Center Study of the Use of the LifePort® Liver Transporter (LLT) System with Vasosol® as Compared to Static Cold Storage in Orthotopic Liver Transplants

(PILOT™: Perfusion to **I**mprove **L**iver **O**utcomes in **T**ransplantation)

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Sponsor:	Organ Recovery Systems
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TABLE OF CONTENTS

Page

1.0 CONTACTS

1.1 Emergency Contacts

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Contact the following individuals for all other inquiries and information about this study:

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2.0 SPONSOR SIGNATURE

My signature, in conjunction with the signature of the investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and applicable laws and other regulations including, but not limited to, the International Council on Harmonization (ICH) Guideline for Good Clinical Practice (GCP), the US Code of Federal Regulations, protections for privacy, and generally accepted ethical principles for human research such as the Declaration of Helsinki.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care.

Sponsor Representative Signature	Date of Signature (DD/MM/YYYY)

Sponsor Representative Name and Title (print)

3.0 INVESTIGATOR SIGNATURES

3.1 Principal Investigator

I have read this protocol and agree that it contains all necessary details to carry out the study as described. I will conduct this protocol as outlined herein, including all statements regarding confidentiality. I will make a reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the Sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational device and the study. I understand that the study may be terminated or enrollment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the interests of the study subjects. Any supplemental information that may be added to this document is also confidential and proprietary to Organ Recovery Systems and must be kept in confidence in the same manner as the contents of this protocol.

I agree to conduct this study in full accordance with all applicable regulations and Good Clinical Practice.

Principal Investigator's Signature	Date of Signature (DD/MM/YYYY)
Principal Investigator's Name (print)	

3.2 Sub-Investigator

I have read this protocol and agree that it contains all necessary details to carry out the study as described. I will conduct this protocol as outlined herein, including all statements regarding confidentiality. I will make a reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the Sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational device and the study. I understand that the study may be terminated or enrollment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the interests of the study subjects. Any supplemental information that may be added to this document is also confidential and proprietary to Organ Recovery Systems and must be kept in confidence in the same manner as the contents of this protocol.

I agree to conduct this study in full accordance with all applicable regulations and Good Clinical Practice.

Sub-Investigator's Signature	Date of Signature (DD/MM/YYYY)
Sub-Investigator's Name (print)	

4.0 DISCLOSURE STATEMENT

4.1 Restricted Distribution of Documents

This document contains information that is confidential and proprietary to Organ Recovery Systems. This information is being provided solely for the purpose of evaluating and/or conducting the clinical trial for Organ Recovery Systems. You may disclose the contents of this document only to study personnel under your supervision, Institutional Review Boards (IRBs), or authorized representatives of regulatory agencies for this purpose under the condition that they maintain confidentiality.

The contents of this document may not be used in any other clinical trial, disclosed to any other person or entity, and/or published without the prior written permission of Organ Recovery Systems. The foregoing shall not apply to disclosure required by any regulations; however, you will give prompt notice to Organ Recovery Systems of any such disclosure.

All other nonpublic information provided by Organ Recovery Systems as well as any information that may be added to this document is also confidential and proprietary to Organ Recovery Systems and must be kept in confidence in the same manner as the contents of this document.

5.0 LIST OF ABBREVIATIONS

Abbreviation	Term
ABO	Antibodies Blood Group
AE	Adverse Event/Adverse Experience
AKI	Acute Kidney Injury
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
BP	Blood Pressure
BMI	Body Mass Index
CFR	Code of Federal Regulations
CIT	Cold Ischemic Time
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
DBD	Donation after Brain Death
DCD	Donation after Cardiac Death
DMP	Data Management Plan
DRI	Donor Risk Index
EAD	Early Allograft Dysfunction
eCRF	Electronic Case Report Form
ECD	Extended Criteria Donor
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FFP	Fresh Frozen Plasma
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HGB	Hemoglobin
HA	Hepatic Artery
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HMP	Hypothermic Machine Perfusion
HTK	Histidine-Tryptophan-Ketoglutarate
ICF	Informed Consent Form
ICU	Intensive Care Unit
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent to Treat
IV	Intravenous
LDH	Lactate Dehydrogenase
LGA	Left Gastric Artery

Abbreviation	Term
LHA	Left Hepatic Artery
LLT	LifePort® Liver Transporter
LSM	Least Squares Mean
MedDRA	Medical Dictionary for Regulatory Activities
MELD-Na Score (lab MELD)	Model for End Stage Liver Disease Score
OLT	Orthotopic Liver Transplantation
PC	Personal Computer
PHI	Protected Health Information
PI	Principal Investigator
PNF	Primary Non-Function
PV	Portal Vein
PP	Per Protocol
PRBCs	Packed Red Blood Cells
RHA	Right Hepatic Artery
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCr	Serum Creatinine
SDV	Source Document Verification
SMA	Superior Mesenteric Artery
SOC	Standard of Care
TBili	Total Bilirubin
UADE	Unanticipated Adverse Device Effect
UNOS	United Network for Organ Sharing
UPS	United Parcel Service
USA or U.S.	United States of America
UW Solution	University of Wisconsin Solution
WIT	Warm Ischemic Time

6.0 SYNOPSIS

Study Title	A Prospective Randomized Multi-Center Study of the Use of the LifePort® Liver Transporter (LLT) System with Vasosol® as Compared to Static Cold Storage in Orthotopic Liver Transplantations (**PILOT**: **P**erfusion to **I**mprove **L**iver **O**utcomes in **T**ransplantation)
Sponsor	Organ Recovery Systems
Investigational Product	LifePort® Liver Transporter (LLT) System and Vasosol® Machine Perfusion Solution
Purpose	To provide reasonable assurance of the safe and effective use of the LLT System with Vasosol® for the preservation of whole explanted livers, thereby confirming the findings of previous clinical studies conducted using a prototype of the LLT System with Vasosol®.
Study Design	Prospective, randomized, multi-center, controlled, comparator study of whole liver preservation via hypothermic machine perfusion (HMP) using the LLT System with Vasosol® and livers preserved via static cold storage (standard of care). Subjects will be randomized using the following stratification: • Model for End Stage Liver Disease (MELD)-Na score (lab MELD): ≤30 or >30 • Donation after cardiac death (DCD): Yes or No
Clinical Phase	Pivotal Study
Number of Sites	A total of eight sites will participate in the study.
Number of Subjects	Study Cohort: Seventy (70) subjects transplanted with whole livers preserved with HMP using the LLT System with Vasosol® Concurrent Control Cohort: Seventy (70) matched subjects transplanted with whole livers preserved with static cold storage
Study Duration per Subject	Subjects will be enrolled in the study for twelve (12) months.
Primary Safety and Effectiveness Outcomes	The primary outcome for this study is the following: 1. Early allograft dysfunction (EAD) defined as presence of one or more of the following: • Total bilirubin ≥10 mg/dL at seven days post-transplant • International normalized ratio (INR) ≥1.6 at seven days post-transplant • Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) >2000 IU/L within seven days of transplant
Secondary Safety and Effectiveness Outcomes	The secondary outcomes of this study are the following: 1. Primary non-function (PNF) defined as relisted for orthotopic liver transplant within seven days of transplant or leading to death within seven days post-transplant without identification of cause such as surgical complications, hepatic artery thrombosis, portal vein

	thrombosis, or acute rejection, and same blood draw taken 24 hours to seven days after transplant showing:
	• AST ≥ 3000 and one or both of the following:
	  o INR ≥ 2.5 or
	  o Acidosis, defined as having arterial pH ≤ 7.30 or venous pH ≤ 7.25 and/or lactate ≥ 4mMol/L
	2. Peak AST, ALT, INR, Serum Creatinine (SCr) and Total Bilirubin (TBili) (every six hours for initial 24 hours, and once daily thereafter) through seven days post-transplant or discharge, whichever occurs earlier.
	3. Acute kidney injury (AKI) based on RIFLE criteria (≥ 2X SCr from baseline or decrease in glomerular filtration rate (GFR) by > 50%; or Urine output < 0.5 mL/kg/hr for ≥ 12 hours) within seven days of transplant
	4. Incidence within three and six months post-transplant of any of the following:
	• Graft failure
	• Biliary complications
	• Vascular complications
	• Subject death

Exploratory outcomes	The exploratory outcomes of this study are the following: 1. Lactate clearance: arterial lactate at 3, 6, 12, 24 hours after reperfusion 2. Time to normality defined as: AST (12–38 IU/mL), ALT (7–41 IU/mL), TBili (0.3–1.3 mg/dL), SCr (0.6–1.12 mg/dL), and INR (0.87–1.16) 3. Time from transplant to hospital discharge [days] 4. Graft failure at 12 months 5. Subject death at 12 months
Key Inclusion Criteria	**For Recipients:** 1. Subject is ≥ 18 years of age 2. Subject is active on the United Network for Organ Sharing (UNOS) waiting list for whole liver transplantation 3. Subject is de novo whole liver transplant recipient 4. Subject is able to read and understand the Informed Consent Form (ICF) and has voluntarily provided written informed consent or, if the subject's condition limits his/her ability to provide consent, written informed consent has been voluntarily provided by the subject's legally authorized representative **For Donors:** <u>All livers suitable for utilization, including:</u> 1. Liver declined by local/regional centers 2. DCD 3. Donor Risk Index (DRI) ≥ 1.6 4. Elevated liver function tests 5. Cardiopulmonary resuscitation (CPR) > 20 minutes

Key Exclusion Criteria	**For Recipients**: 1. Subject is <18 years of age 2. Subject is a multi-organ transplant recipient 3. Subject is previous liver transplant recipient 4. Subject is antibodies blood group (ABO) liver incompatible 5. Subject has severe systemic infection 6. Subject is Human Immunodeficiency Virus (HIV) positive 7. Subject has acute/fulminant liver failure (defined as rapid development of acute liver failure with severe impairment of synthetic function and hepatic encephalopathy without obvious previous liver disease) 8. Subject is pregnant 9. Subject or subject's legally authorized representative declines study participation and/or refuses to provide informed consent **For Donors**: 1. Donor is HIV positive 2. CIT is <3 hours anticipated
Statistical Analysis For Primary Endpoint	The incidence rates of EAD between the test arm using the LLT System and the control arm will be compared to demonstrate that EAD incidence is within a clinically reasonable margin. Specifically, the following hypothesis is being tested: $H_0: \mathrm{EAD}_{LLT} - \mathrm{EAD}_{Control} > \delta$ vs. $H_a: \mathrm{EAD}_{LLT} - \mathrm{EAD}_{Control} \leq \delta$ where EAD indicates EAD incidence rate and δ is the non-inferiority margin. The hypothesis will be tested by evaluating whether the upper limit of the one-sided 95% confidence interval for the difference in incidence rates is smaller than or equal to δ. Point estimates and 95% confidence intervals (CIs) for incidence rates will be provided by study arm along with point estimates and 95% CIs for differences in incidence rates between the study arms.
Additional Statistical Analyses	Summary statistics for all demographic and baseline variables for the test and control arms will be provided to demonstrate that subjects enrolled in this study are representative of the Intended Use population. For all binary outcomes, point estimates and 95% CIs for incidence rates will be provided by study arm along with point estimates and 95% CIs for differences in incidence rates between the study arms. For continuous outcomes, point estimates and 95% CIs for Least Squares means (LS means) will be provided by study arm along with point estimates and 95% CIs for differences in LS means between the study arms. A detailed description of all statistical methods will be provided in a separate Statistical Analysis Plan (SAP) that will be finalized prior to database lock.
Acceptance Criterion	A non-inferiority margin δ of 7.5% will be considered as a clinically relevant margin to show non-inferiority.

Sample Size Justification	Incidence rates for the test arm and the control arm were assumed to be 15% and 30%, respectively, based on published results (Guarrera et al. 2010, Guarrera et al. 2015, Olthoff et al. 2010). Based on the statistical analysis and acceptance criterion outlined above and an estimated attrition rate of 10%, a sample size of 70 subjects per study arm is sufficient to demonstrate non-inferiority at 80% power with a non-inferiority margin δ of 7.5% using a frequentist approach.

7.0 SCHEDULE OF STUDY EVENTS

Table 7.1 - Study Flowchart of Scheduled Events

Event	Screening and Enrollment (Day -7 to 0)[1]	Baseline Visit (Day -7 to 0) [1]	Liver Transplant/Visit 1 (Day 0)	Visits 2-8 (Days 1-7)[2]	Visits 9 & 10 (3 Months ± 7 Days; 6 ± 1 Month)	Visit 11 (12 ± 1 Month)	Early Termination[3]
Informed Consent	X						
Inclusion/Exclusion Criteria	X						
Demographics		X					
Medical History		X					
Physical Exam		X	X[7]	X	X		X
MELD-Na Score (lab MELD)		X					
Clinical Laboratory Tests		X[8]	X[7,9,10]	X[11]	X[12]		X[12]
Vital Signs[4]			X	X	X		X
Randomization	X						
Liver Transplant Procedure			X				
Liver Biopsy[5]		X	X				
Radiographic Studies[6], Post-Op Monitoring[13]			X	X	X		X
Adverse Events			X	X	X		X
Subject Status[14]				X	X	X	X
Study Completion						X	X

[1] Screening and enrollment and baseline visits may take place on the same day as transplant (Day 0), depending on when the subject is scheduled for surgery.

[2] Visits 2-8 will take place on post-transplant days 1-7 of the study while the subject is hospitalized. The same study assessments will be conducted on each of these visits as noted in the above table. If subject is discharged prior to Day 7 and unable to return for Day 7 visit, labs drawn ±2 days of Day 7 may be used.

[3] Assessments to be completed to the extent possible if the subject is an early withdrawal.

[4] Vital signs will include body temperature, heart rate, systolic and diastolic blood pressure, mean arterial pressure (MAP), and respiratory rate.

[5] Liver biopsy will be obtained from donor liver pre-preservation, post-preservation, and a minimum of 60 minutes post-arterial reperfusion during transplant procedure.

[6] Post-transplant chest x-ray and Doppler ultrasound imaging will be performed on Day 0. Additional radiographic studies and Doppler ultrasounds will be completed according to standard of care and as medically indicated to assess liver health per the investigator's discretion.

[7] If the liver transplant procedure takes place on the same day as baseline (within 24 hours), then the baseline physical exam and clinical laboratory tests will serve as the pre-procedure assessments.

[8] Clinical laboratory data to be collected at baseline (Day -7 to 0) include:

- Chemistry: sodium, potassium, chloride, bicarbonate, BUN, SCr, calculated GFR, AST, ALT, alkaline phosphatase, TBili, total protein: albumin/globulin ratio (calculated) and lactate
- Hematology: white blood cells (WBC), absolute neutrophil count (ANC), hemoglobin (HGB), hematocrit (HCT) and platelets

- Coagulation: prothrombin time (PT) and international normalized ratio (INR)

[9] Clinical laboratory data to be collected pre-transplant on Day 0 (Visit 1) *(labs required if baseline visit not conducted within 24 hours of transplant)* include:

- Chemistry: sodium, potassium, chloride, bicarbonate, BUN, SCr, calculated GFR, AST, ALT, alkaline phosphatase, TBili, total protein: albumin/globulin ratio (calculated)
- Hematology: WBC, ANC, HGB, HCT and platelets
- Coagulation: PT and INR

[10] Clinical laboratory data to be collected post-transplant on Day 0 (Visit 1) include:

- Chemistry: AST, ALT, INR, SCr, and TBili will be collected every 6 hours for the initial 24 hours
- Arterial Lactate: collected at 3, 6, 12 and 24 hours post-transplant

[11] Clinical laboratory data to be collected on Days 1 through 7 (Visits 2-8) or until discharge, whichever occurs earlier. (*If the subject is discharged prior to post-transplant day 7, the subject will be asked to return on Day 7 for study visit and blood draw. If the subject is unable to return for the Day 7 visit (Visit 8), labs drawn ±2 days of Day 7 may be used.*)

- Chemistry: sodium, potassium, chloride, bicarbonate, BUN, SCr, calculated GFR, AST, ALT, alkaline phosphatase, TBili, total protein: albumin/globulin ratio (calculated) and lactate
- Hematology: WBC, ANC, HGB, HCT and platelets
- Coagulation: PT and INR
- Venous pH and/or arterial pH will only be collected post-transplant day 1 through 7 as needed to assess PNF (if AST $\geq$ 3000)

[12] Clinical laboratory data to be collected at 3 and 6 Months (Visits 9 and 10), and at the Early Termination Visit (if applicable), includes:

- Chemistry: sodium, potassium, chloride, bicarbonate, BUN, SCr, calculated GFR, AST, ALT, alkaline phosphatase, total protein: albumin/globulin ratio (calculated) and lactate
- Hematology: WBC, ANC, HGB, HCT, platelets
- Coagulation: PT and INR

[13] Standard of care radiographic studies and/or Doppler studies will be recorded if completed. A summary of the key findings of these studies will be documented. Post-op monitoring will include urine output while hospitalized to assess AKI through post-transplant Day 7.

[14] Subject status will be documented with respect to graft status (failure or function) and subject status (alive or deceased).

8.0 ETHICAL CONSIDERATIONS

This clinical study is designed to comply with the International Council on Harmonization (ICH) E6(R1) Good Clinical Practices (GCP), Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice (ISO14155:2011), and applicable governing United States Food and Drug Administration (FDA) regulations including: the protection of human subjects (21 CFR 50 and 45 CFR 46); financial disclosure by clinical investigators (21 CFR 54); Institutional Review Boards (21 CFR 56), including local or central IRB requirements; and Investigational Device Exemptions (21 CFR 812).

8.1 Institutional Review Board

It is the responsibility of the Investigator to obtain the approval of the IRB before the start of the study. The IRB must be registered and active with the Office for Human Research Protections of the US Department of Health and Human Services. A copy of the approval letter along with a roster of IRB members and/or the US Department of Health and Human Services general assurance number will be retained as part of the study records. During the course of the study, the Investigator will provide timely and accurate reports to the IRB on the progress of the study at appropriate intervals (not to exceed one year) and at the completion of the study. The Investigator will notify the IRB of serious adverse events (SAEs) or other significant safety findings per IRB guidelines. The study protocol, ICF, advertisements (if any), and amendments (if any) will be approved by the IRB in conformance with 21 CFR 56.

8.2 Ethical Conduct of the Study

The study will be conducted in full compliance with applicable FDA regulations and ICH guidelines for GCP and in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

8.3 Data and Safety Monitoring Board (DSMB)

A DSMB will be organized to safeguard the interests of the subjects enrolled in this study and to assess the safety of the interventions during conduct of the study. The DSMB will be a multidisciplinary group composed of independent and qualified individuals who specialize in the field of study. The DSMB will advise the Sponsor on the appropriateness of continuing the study based on an independent evaluation of safety.

8.4 Subject Informed Consent

The study will not begin until the ICF documents have been approved by the IRB(s). The ICF shall contain all of the elements of informed consent specified in the Code of Federal Regulations (21 CFR 50.25) and a HIPAA authorization form. Copies of the regulations relating to informed consent and the protection of human subjects in clinical studies are available from the Sponsor.

All potential study subjects will be given copies of the following before participating in any study-specific procedures:

- The study ICF;
- Site-required informed consents and agreements for HIPAA Authorization;

- Any specific documentation that may be required by the site's IRB.

The subject or subject's representative will have an opportunity to discuss the contents of these forms with study site staff. The study should be thoroughly explained including the purpose of the study, methods, anticipated benefits, and potential hazards prior to obtaining written consent.

The subject or subject's representative must understand and voluntarily sign these forms in compliance with 21 CFR Parts 50 and 812, before participating in any study-related procedures. Subjects will be made aware that they may withdraw from the study at any time.

The subject will be made aware of his/her right to see and copy his/her records related to the study for as long as the Investigator has possession of this information. If the subject withdraws consent and/or HIPAA authorization, the Investigator can no longer disclose health information, unless it is needed to preserve the scientific integrity of the study. A copy of the informed consent document will be given to the subjects for their records.

The subjects will also be informed that their medical records may be reviewed by the study Sponsor or designee, quality assurance auditor, or inspector from FDA. The subjects will be informed that these persons are bound by the same confidentiality obligations as the subject's physician.

Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care under applicable regulations. Regulations require that Investigators permit the Sponsor, Sponsor representatives, and appropriate regulatory agencies to conduct inspections and review records pertaining to clinical investigations.

The delegation of Investigator responsibilities, including obtaining informed consent, must be documented in the study records.

8.5 Subject Confidentiality

The Principal Investigator and designees, employees, and agents involved with this study will comply with relevant state and federal laws relating to the confidentiality, privacy, and security of subject's PHI. They will only create, maintain, use, or disclose any data that is generated by this study or other information disclosed to the Principal Investigator or their employees or agents during the course of the study to the Sponsor, IRB, FDA, or other authorized recipients as appropriate for the execution, analysis, review, and reporting of this study. Such information shall not be used for any other purposes and will remain confidential.

Subject records are only to be identified by site ID and subject ID numbers. Subject names are not to be transmitted on any document to the Sponsor.

9.0 INTRODUCTION

9.1 Background and Current Treatment

For at least two decades, static cold storage of donor livers has been the standard of care for orthotopic liver transplantation (OLT).[1] OLT after cardiac death or from elderly or steatotic donors, however, carries higher risks of serious post-transplantation complications, including re-transplantation and death. Kidney transplants, however, commonly utilize HMP, in which a preservation solution is continuously circulated through the donor kidney, acting to preserve normal homeostasis as well as allowing for pre-transplant preparation for transplantation. Initial testing of HMP use in liver transplantation in animals and humans shows promising results and warrants further investigation of the safety and efficacy of this preservation method.[1-3]

9.2 LifePort® Liver Transporter (LLT) System with Vasosol®

The LLT System is a portable, isolated liver perfusion and transport system, designed to support a donated liver and to maintain the organ in a near-normal physiologic state under hypothermic aseptic conditions, while simultaneously perfusing the liver until it is transplanted into a recipient patient.

The LLT System and Vasosol® Machine Perfusion Solution are for investigational use only.

9.3 Completed Studies with the LLT System with Vasosol®

9.3.1 Matched Control Pilot Study

This study, the first prospective study which evaluated the use of HMP in OLT, was conducted between 2004 and 2008 in patients undergoing isolated primary OLT.[1] In this pilot study 20 adults who received donor livers preserved with HMP (3-7 hours perfusion with Vasosol®) were compared to matched subjects who received livers preserved by static cold storage. EAD rates were 5% in the HMP group as compared to 25% among controls; serum injury markers were significantly lower in the HMP group as well, as was mean hospital stay. Four biliary complications occurred in the static cold storage group compared to two in HMP subjects. At 12 months, there was a total of two deaths in each group, none related to graft function. This case-controlled study demonstrated that HMP preservation with Vasosol® was an effective and safe method of augmenting preservation in liver transplantation, warranting further clinical trials.

9.3.2 Extended Criteria Donor Matched Control Study

This study evaluated 31 subjects,[2] including 7 subjects from the previous study, who had received HMP-perfused extended criteria donor (ECD) livers who were compared in a matched cohort study design with ECD livers preserved by static cold storage. Livers were matched for both donor and recipient age as well as cold ischemic time, donor risk index and MELD score. HMP consisted of perfusion for 3-7 hours at 4-8°C. Subjects who received HMP-preserved livers had higher survival rates (85% vs 80%) than those who had received livers in static cold storage, lower rates of early allograft dysfunction (19% vs 30%, respectively), and significantly fewer biliary complications (4% in HMP subjects compared to 13% in subjects with static cold storage organs).

9.4 Potential Risks and Benefits of this Study

9.4.1 Potential Risks

A prototype of the LLT System with Vasosol® has been evaluated in 44 subjects for the same purpose of HMP preservation of livers, as summarized above in **Section 9.3**. Results of these studies demonstrated no serious adverse events attributable to HMP preservation with Vasosol®.

Anticipated risks and complications associated with liver transplant, regardless of use of machine perfusion, are numerous and include, but are not limited to: anatomic graft injury during preservation or implant including severe preservation injury, primary non-function (PNF), early allograft dysfunction (EAD), ischemic injury, vascular complications (e.g., hepatic artery thrombosis, portal vein thrombosis, major bleeding requiring re-intervention), biliary complications (e.g., leakage, stricture), acute kidney injury and chronic kidney disease, elevated portal pressures, infection, abdominal abscess, cholestasis, thrombocytopenia, incisional hernia, graft rejection, graft failure, and subject death.

One of the potential device-related risks of HMP is mechanical failure of the LLT System. The LLT System is continuously monitored by technical and surgical staff, and in the unlikely event of mechanical failure, prompt conversion to static cold storage would occur, which is standard of care.

Another small but potential risk related to HMP is vascular injury to the liver due to cannulation of liver vessels for perfusion. This complication did not occur in the previous studies and the likelihood is low given the expertise of transplant team members.

Liver biopsies will be obtained pre-preservation, post-preservation, and a minimum of 60 minutes post-arterial reperfusion during the transplant procedure, therefore there is a risk of bleeding or hematoma at the liver biopsy sites. Liver biopsies are commonly performed during transplant procedures, and open biopsy complications are rare.

There is a possibility that HMP preservation using the LLT System with Vasosol® may be inferior to standard of care static cold storage using a marketed preservation solution. Based on results of previous clinical studies of use of HMP with Vasosol®, and published literature on machine perfusion for organ preservation, there are no known biological or mechanistic factors that would result in inferior preservation using the LLT System with Vasosol® as compared to static cold storage. Regardless of method of preservation, acceptability of use of the preserved liver remains at the discretion of the transplanting surgeon.

9.4.2 Potential Benefits

Subjects whose liver grafts are preserved with the LLT System with Vasosol® may benefit by improved preservation and less ischemia/reperfusion injury to the liver, resulting in improved early liver function and quality. In turn, improved early function and fewer complications could result in a shorter duration of Intensive Care Unit (ICU) care and/or hospital length of stay from time of transplant.

Potential benefits to society include improvement in organ utilization (with greater use of organs considered marginal and fewer livers discarded) and improved results of liver transplantation.

9.5 Rationale for This Study

The previous studies which evaluated the use of HMP with the LLT System confirmed the efficacy and safety of a prototype of the LLT System with Vasosol® for liver transplantation. This study is being initiated in order to evaluate the safety and effectiveness of the to-be-marketed LLT System with Vasosol® in order to confirm previous clinical findings.

10.0 OBJECTIVES

10.1 Primary Objective

The primary objective of this study is to collect clinical data to provide reasonable assurance of safe and effective use of the LLT System with Vasosol® for the preservation of explanted livers, confirming findings of previous clinical studies conducted using a prototype of the LLT System with Vasosol®.

11.0 STUDY DESIGN

This study is a prospective, randomized, controlled study comparing hypothermic machine perfusion (HMP) of explanted livers as compared to control livers preserved via static cold storage (standard of care). The schedule of study events lists the procedures to be performed in each visit (see **Table 7.1**).

11.1 Measures Taken to Avoid Bias

11.1.1 Randomization

Subjects meeting the study eligibility criteria and providing written informed consent will be prospectively enrolled into the LLT System group prior to their liver transplant procedure. After initial acceptance by the transplant team for the recipient, the recipient will be randomized to receive a liver preserved via static cold storage (standard of care) or via HMP using the LLT System. Stratified randomization will be performed by lab MELD score and DCD liver type to balance the treatment and control groups as follows:

- Model for End Stage Liver Disease (MELD)-Na score (lab MELD): ≤30 or >30; and
- Liver donation after cardiac death (DCD): Yes or No.

Stratification factors of MELD-Na score category (≤30 or >30) and liver type (DCD Y/N) will be considered as one factor with four levels (strata). The four levels or strata are: MELD ≤30 and DCD Y; MELD ≤30 and DCD N; MELD >30 and DCD Y; and MELD >30 and DCD N. Within each strata, treatment assignments will be periodically balanced, and the assignments independent of each other. At the end of the study, the treatment assignments in each stratum will be roughly balanced, yielding balance of the strata across the two treatment arms of liver preservation via HMP and liver preservation via standard cold storage.

Each randomized subject will receive a unique randomization number, and randomization will be performed utilizing the built-in randomization feature of the electronic data capture (EDC) system.

11.1.2 Blinding

Neither subjects nor investigators will be blinded. The central, independent pathologist analyzing the liver biopsy samples will be blinded to the method of preservation.

11.2 Description of the Study Device

The LLT System provides portable perfusion of the hepatic artery and portal vein and includes real-time monitoring of organ status and performance, including perfusate flow and pressure and perfusion status. The device is used to perfuse donor livers with Vasosol®, a solution with composition consistent with that of an extracellular solution (approximate calculated osmolality of 300 mOsm/kg, sodium concentration of 100 mEq/L, potassium concentration of 25 mEq/L, and pH of approximately 7.4 at room temperature).

12.0 SELECTION OF STUDY POPULATION

Subjects will be recruited from patients undergoing isolated primary orthotopic whole liver transplantation. The inclusion and exclusion criteria defining the patient populations to be studied apply across all subpopulations listed with the United Network of Organ Sharing (UNOS) for liver transplantation at the respective investigational sites. Liver preservation with the LifePort® Liver Transporter System with Vasosol® is available to all minorities, including African American and Hispanic patients, and women, who are enrolled in the study and randomized to the treatment arm. These patient populations, often underrepresented in clinical studies, will not be prohibited from entering into this study provided that they meet the study inclusion and exclusion criteria.

The results of this study are expected to be generalizable to the Medicare population based on the study inclusion and exclusion criteria, and because all investigational sites are in the United States. It is anticipated that the subjects in this study will be representative of the patients who require liver transplantation such that the findings from the study should be generalizable to the population of patients so afflicted. This includes Medicare beneficiaries who qualify because of disability, age, or end-stage renal disease.

12.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to participate in this study:

For Recipients:
1. Subject is ≥18 years of age
2. Subject is active on the UNOS waiting list for whole liver transplantation
3. Subject is de novo whole liver transplant recipient
4. Subject is able to read and understand the ICF and has voluntarily provided written informed consent, or, if the subject's condition limits his/her ability to provide consent, written informed consent has been voluntarily provided by the subject's legally authorized representative

For Donors: <u>All livers suitable for utilization, including:</u>
1. Liver declined by local/regional centers
2. DCD
3. DRI ≥ 1.6
4. Elevated liver function tests
5. CPR > 20 minutes

12.2 Exclusion Criteria

Any subject who meets any of the exclusion criteria will be excluded from participation in this study:

For Recipients:
1. Subject is <18 years of age
2. Subject is a multi-organ transplant recipient
3. Subject is a previous liver transplant recipient
4. Subject is antibodies blood group (ABO) liver incompatible
5. Subject has severe systemic infection

6. Subject is HIV positive
7. Subject has acute/fulminant liver failure (defined as rapid development of acute liver failure with severe impairment of synthetic function and hepatic encephalopathy without obvious previous liver disease)
8. Subject is pregnant
9. Subject or subject's legally authorized representative declines study participation and/or refuses to provide informed consent

For Donors:

1. Donor is HIV positive
2. CIT is <3 hours anticipated

12.3 Subject Withdrawal

Subjects may discontinue from the study at any time. A subject may be discontinued from the study for the following medical or administrative reasons:

- **Donor liver declined prior to transplant** - Original designated recipient does not undergo liver transplantation. The timing of withdrawal (pre- or post-preservation) will be documented.
- **Subject Withdrawal of Consent –** Subjects will be free to discontinue from the study at any time and for any reason but must notify the study site of their exit from the study.
- **Adverse Event –** If during the procedures the subject suffers an AE that, in the judgment of the Principal Investigator (PI), Sponsor or Medical Monitor, presents an unacceptable consequence or risk to the subject, the subject will be discontinued from further participation in the study.
- **Lost to Follow Up –** Subjects discontinue from the study without notifying the study site.
- **Serious Protocol Violation –** If, during enrollment in the study, the subject fails to follow, violates, or refuses to participate in any of the procedures described in the protocol, then the subject will be discontinued from the study due to protocol violation. If, at any point during the study, a subject is determined to have been erroneously enrolled into the study, the subject will be discontinued from the study due to protocol violation.
- **Other –** If the above reasons are not applicable, "Other" will be selected as the option and the appropriate reason for subject withdrawal provided.

For subjects who discontinue or are withdrawn from the study for any reason, the PI will notify the Sponsor and will be required to attempt to determine whether any AE occurred since the last visit to the study site.

If the subject is withdrawn at a study visit, the procedures for an early termination visit will be conducted including an exit physical exam to assess their continued well-being.

13.0 STUDY PROCEDURES

No protocol-specific procedures will be performed until the subject has signed and dated an IRB-approved informed consent form.

13.1 Subject Identification

Each subject, regardless of treatment group, will be assigned a unique subject number. Subject numbers will not be reassigned or reused for any reason. Only their assigned subject number and date of birth should identify subjects to the Sponsor. The Investigator will maintain a list of potential subjects and enrolled subjects using the Subject Screening/Enrollment Log.

Any potential subjects who are pre-screened can be added to the log by recording their screening number. Those who sign the ICF will be assigned a five-digit sequential number. The first two digits will represent the site number (i.e., 01) and the remaining three digits are a sequential subject number (i.e., 001, 002, 003, etc.). Therefore, the fourth subject screened at site number one will be Subject #01004.

13.2 Subject Enrollment

Subjects who meet all inclusion and exclusion criteria and who are being offered a liver from a donor who meets all inclusion and exclusion criteria will be considered eligible for enrollment. Subjects will be considered enrolled on Day 0 upon randomization of preservation method. Once enrolled, a subject may only exit the study as a withdrawal (not a screen failure). The reason for withdrawal will be documented by the Investigator on the Subject Screening/Enrollment Log. Electronic case report forms (eCRFs) will be completed for all enrolled subjects.

The data required for control subjects are identical to the data required for the LLT System subjects. Additional investigational device-specific information such as perfusion time, flow rate and temperature of perfusate will be recorded for subjects in the HMP group.

13.3 Subject Randomization

After initial acceptance by the transplant team for the recipient, the recipient will be randomized to receive a liver preserved via static cold storage (standard of care) or via HMP using the LLT System. Stratified randomization will be performed by MELD-Na score (lab MELD) and DCD liver type to balance the treatment and control groups as follows:

- Recipient Model for End Stage Liver Disease (MELD)-Na score (lab MELD): ≤30 or >30; and
- Liver donation after cardiac death (DCD): Yes or No.

Each randomized subject will receive a unique randomization number, and randomization will be performed utilizing the built-in randomization feature of the EDC system. Specifically, a randomization order will be generated prior to the start of the study to balance enrollment across randomization strata.

Note: If the originally designated study recipient does not undergo transplantation of the assigned liver, the subject will be withdrawn from the study. If the liver is reallocated to another matched recipient at the same site or at another site participating in the study who

consents to study participation, the recipient to whom the liver is reallocated will be assigned a unique subject identification number and be followed as a substudy subject. Re-randomization will not occur for reallocated livers.

13.4 Screen Failures

Subjects who sign an ICF and fail to meet the inclusion and/or exclusion criteria are defined as screen failures. For all screen failures, the Investigator will record the reason for the screen failure on the Screening/Enrollment Log. A copy of the log will be retained in the investigator's study files.

13.5 Description of Study Procedures

13.5.1 Clinical Laboratory Tests

Clinical laboratory tests to be evaluated in this study include hematology, serum chemistry, coagulation and venous and/or arterial pH. Blood samples will be obtained according to the Schedule of Events (**Table 7.1**) and in accordance with NIH blood volume limits. For blood draws that are obtained during the follow up visits, subjects should be reminded not to exercise prior to their visit. All samples will be analyzed locally at each site, with their respective reference standards documented.

Table 14.1 shows the parameters to be assessed:

Table 14.1 - Listing of Required Clinical Laboratory Tests

Laboratory Panel	Laboratory Test
Hematology[1]	White blood cells (WBC), absolute neutrophil count (ANC), Hemoglobin (HGB), hematocrit (HCT) and platelets
Serum Chemistry[2]	Sodium, potassium, chloride, bicarbonate, BUN, SCr, calculated GFR, AST, ALT, alkaline phosphatase, TBili, total protein: albumin/globulin ratio (calculated) and lactate
Coagulation[3,4]	Prothrombin time (PT) and international normalized ratio (INR)
Venous and/or Arterial Blood Gas[5]	Venous pH, arterial pH

[1] Hematology data will be collected as follows: Baseline Visit (Day -7 to 0); Transplant/Visit 1 (Pre-Transplant Day 0), if Baseline Visit not conducted within 24 hours of transplant; Visits 2 through 8 (Days 1 through 7 Post-Transplant) or until discharge, whichever occurs earlier; Visits 9 and 10 (3 and 6 Months Post-Transplant); and at the Early Termination Visit/Visit 11 (if applicable).

[2] Serum Chemistry data will be collected as follows: Baseline (Day -7 to 0); Transplant/Visit 1 (Pre-Transplant Day 0) except lactate, if Baseline Visit not conducted within 24 hours of transplant; Transplant/Visit 1 (Post-Transplant Day 0), AST, ALT, SCr, and TBili will be collected every 6 hours for the initial 24 hours, and arterial lactate will be collected at 3, 6, 12 and 24 hours post-transplant; Visits 2 through 8 (Days 1 through 7 Post-Transplant), or until discharge, whichever occurs earlier; Visits 9 and 10 (3 and 6 Months Post-Transplant); and at the Early Termination Visit (if applicable).

[3] Coagulation data will be collected as follows: Baseline Visit (Day -7 to 0); Transplant/Visit 1 (Pre-Transplant Day 0), if Baseline Visit not conducted within 24 hours of transplant; Transplant/Visit 1 (Post-Transplant Day

0) INR will be collected every 6 hours for the initial 24 hours; Visits 2 through 8 (Days 1 through 7 Post-Transplant) or until discharge, whichever occurs earlier); Visits 9 and 10 (3 and 6 Months Post-Transplant); and at the Early Termination Visit/Visit 11 (if applicable).

[4] For PT and INR, blood should be drawn prior to the administration of anti-coagulant therapy.

[5] Venous pH and/or arterial pH will be collected as follows: Visits 2 through 8 (Days 1 through 7 Post-Transplant) or until discharge, whichever occurs earlier, as needed to assess PNF (if AST ≥ 3000).

13.5.2 Liver Biopsy

Liver biopsies will be obtained pre-preservation, post-preservation, and post-reperfusion. Needle biopsies of the donor liver will be obtained pre-preservation by the procuring surgeon for RNA*later*™ and formalin storage, and post-preservation for RNA*later*™ storage. Needle biopsies of the liver will also be obtained a minimum of 60 minutes post-arterial reperfusion during the transplant procedure, also for RNA*later*™ and formalin storage. Tissue samples will be analyzed by a central, independent, experienced pathologist who will be blinded to the method of liver preservation (HMP or static cold storage). Samples will undergo pathological examination including assessment of macrovesicular steatosis, ischemic injury, cholestasis, central fibrosis, Batts Ludwig classification, and Suzuki Score. The biopsy results from both treatment groups will be compared for signs of disease and damage. Samples stored in RNA*later*™ may undergo analysis for further assessments, including determining the levels of standard enzyme markers for injury.

13.5.3 Vital Signs

Vital signs will include body temperature, heart rate, systolic and diastolic blood pressures, mean arterial blood pressure (auto calculated), and respiratory rate. Heart rate should be measured immediately before or immediately after blood pressure measurement.

Vital signs will be measured at baseline (prior to liver transplant procedure), at 0.5, 1, and 2 hours post-transplant, at post-transplant days 1 through 7 (Visits 2-8) or until discharge, at 3 and 6 months (Visits 9 and 10) and at early termination (Visit 11) if applicable.

13.5.4 Physical Exam

Physical examinations will be conducted according to the Schedule of Events (**Table 7.1**) and will include the following:

- Height
- Weight
- Body mass index (BMI)
- General appearance
- Skin/dermatological
- Neurological
- Cardiovascular
- Respiratory
- Gastrointestinal
- Genitourinary

Normal/abnormal findings will be documented, and any abnormal findings will be characterized as pre-existing, new onset, or ongoing.

Any new clinically significant physical exam findings will be followed by a physician or qualified staff at the next scheduled visit or as medically indicated.

13.5.5 MELD-Na Score (Lab MELD)

The MELD-Na (Model for End-Stage Liver Disease) score or lab MELD is a scoring system used to numerically assess the severity of chronic liver disease in order to prioritize donor liver receipt. The score combines the values for bilirubin, SCr, INR, and serum sodium in order to assess severity of chronic liver disease. This assessment will be performed as part of screening, using values taken within 48 hours and recorded as 'MELD-Na score (lab MELD) at time of transplant' on the study eCRF. The lab MELD-Na score determined at time of organ offer, based on UNOS allocation labs, will be used for randomization stratification, and also recorded on the eCRF.

13.5.6 Radiographic Studies, Liver Biopsy and Post-Op Monitoring

The pattern of liver function test results are monitored for early signs of dysfunction, which may require intervention. Unexpected values may result in a series of tests which may include Doppler ultrasound to evaluate the patency of the new liver, bile duct studies to evaluate any abnormality of the biliary system, and liver biopsy to rule out rejection. Post-transplant chest x-ray and Doppler ultrasound imaging will be performed. Additional radiological studies will be conducted according to standard care and as medically indicated. Monitoring fluid and electrolytes and maintaining patency of draining tubes is part of the site's standard of care for monitoring post-op patients.

13.6 Procedures To Be Conducted at Each Study Site Visit

13.6.1 Screening and Enrollment and Baseline (Day -7 to 0)

The screening period of the study will take place up to seven days prior to enrollment. Potential subjects will be notified that a liver is available and their intended donor liver potentially confirmed as study-eligible based on the donor inclusion/exclusion criteria. Potential subjects will receive initial study documents including the ICF. Subjects or their authorized representative will be given ample time to review and ask any questions about the clinical trial prior to signing informed consent.

Screening and Enrollment Visit Tasks and Data Collection

- Informed consent
- Inclusion/exclusion criteria
  The collected data will include date of eligibility (confirmed by Investigator), confirmation that each inclusion/exclusion criterion has been met and the date of informed consent/enrollment.

Baseline Visit Tasks and Data Collection

Once informed consent is obtained, eligibility of the subject (i.e., recipient) and the donor liver will be confirmed according to inclusion and exclusion criteria, and the tasks and data collection listed below will be performed.

- Date of baseline assessment
- Demographics of donor
  Donor demographic data will include date of birth, donor age at the time of donation, gender, race/ethnicity and UNOS ID.
- Demographics of recipient
  Recipient demographic data will include date of birth, recipient age at the time of transplant, gender, race/ethnicity, UNOS Waiting List ID and the UNOS listing date, and whether the donor liver was declined by local/regional centers, and if so, reason if known.
- Medical history of donor
  The medical history of the donor will be collected, as available. This information may include significant comorbidities, height, weight, body mass index (BMI) (auto calculated), ABO blood group, Rh factor, DRI, hospital length of stay, length of required ICU care, CPR duration (if applicable), and donor type (e.g., DCD or donation after brain death [DBD]). For DCD donors, the cause of death, date and time of death will be documented. The donor's hepatitis status (Hepatitis B virus [HBV] and Hepatitis C Virus [HCV]), history of cytomegalovirus (CMV), peak (within 7 days of procurement) and terminal Na^+ level and liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], and total bilirubin [TBili]) will be documented as available, as well as pressor agents used immediately prior to procurement and the lowest recorded BP within 7 days of procurement.
- Pre-preservation donor liver biopsies
  Needle biopsies for RNA*later*™ and formalin storage will be performed by the procuring surgeon for analysis by a central, independent pathologist. Samples stored in RNA*later*™ may undergo analysis for further assessment (optional) to determine the levels of standard enzyme markers for injury. The following will be documented:

  - Macrovesicular Steatosis
    - 0-10% (mild)
    - 11-20% (mild)
    - 21-30% (mild)
    - 31-40% (moderate)
    - 41-50% (moderate)
    - 51-60% (moderate)
    - > 60% (severe)
  - Ischemic Injury (severity/ type)
    - Absent
    - Present
      - Coagulative necrosis
      - Mild (single necrotic hepatocytes)
      - Moderate (small groups of necrotic hepatocytes)
      - Severe (large area of necrotic hepatocytes)
  - Cholestasis
    - None
    - Mild

  - Moderate
  - Severe
- Central Fibrosis
  - Absent
  - Present
    - Sinusoidal ("chicken wire")
    - Perivenular
- Batts-Ludwig Classification

Staging of Chronic Hepatitis (single score from 0 to 4)

Staging Terminology		
Semi-quantitative	**Descriptive**	**Criteria**
0	No fibrosis	Normal connective tissue
1	Portal fibrosis	Fibrosis portal expansion
2	Periportal fibrosis	Periportal or rare portal-portal septa
3	Septal fibrosis	Fibrous septa with architectural distortion; no obvious cirrhosis
4	Cirrhosis	Cirrhosis

Grading of Disease Activity in Chronic Hepatitis (single score from 0 to 4)

Grading Terminology		Criteria	
Semi-quantitative	**Descriptive**	**Lymphocytic piecemeal necrosis**	**Lobular inflammation and necrosis**
0	Portal inflammation only; no activity	None	None
1	Minimal	Minimal; patchy	Minimal; occasional spotty necrosis
2	Mild	Mild; involving some or all portal tracts	Mild; little hepatocellular damage
3	Moderate	Moderate; involving all portal tracts	Moderate; with noticeable hepatocellular change
4	Severe	Severe; may have bridging fibrosis	Severe; with prominent diffuse hepatocellular damage

- Suzuki Assessment Score: A score of 0 to 4 will be assigned for each of the following: sinusoidal congestion, cytoplasmic vacuolization (ballooning degeneration), and hepatic necrosis; total score will range from 0 to 12.

Suzuki Score (total score from 0 to 12)

Score	Sinusoidal Congestion	Cytoplasmic Vacuolization	Hepatic Necrosis
0	None	None	None
1	Minimal	Minimal	Single Cell Necrosis
2	Mild	Mild	<30%
3	Moderate	Moderate	≤60%
4	Severe	Severe	>60%

- Medical history of recipient
  The medical history of the recipient will include liver failure etiology, significant comorbidities, ABO blood group, Rh factor, hospital length of stay and length of required ICU care. The recipient's hepatitis status HBV and HCV, including HBsAG, anti-HBc and anti-HBs, and history of CMV will be documented.
- Recipient Assessments and Laboratory Tests
  The recipient's MELD-Na score (lab MELD) at time of organ offer as well as at time of transplant (within 48 hours of transplant) will be documented. Chemistry data including sodium, potassium, chloride, bicarbonate, BUN, SCr, calculated GFR, AST, ALT, alkaline phosphatase, TBili, total protein: albumin/globulin ratio (calculated), and lactate will be collected. Hematology data including WBC, ANC, HGB, HCT and platelets will be collected. Coagulation data including PT and INR will be collected.
- Physical exam
  Physical exam will include height, weight, BMI (auto calculated) and assessments of general appearance and skin/dermatological, neurological, cardiovascular, respiratory, gastrointestinal, and genitourinary systems.

13.6.2 Liver Transplant/Visit 1 (Day 0)

Subjects who consent and meet all inclusion/exclusion criteria will be enrolled in the study prior to the liver transplant procedure. The screening and enrollment and baseline visits may be on the same day (within 24 hours) as the liver transplant procedure.

After initial acceptance by the transplant team for the recipient, the recipient will be randomized to receive a liver preserved via static cold storage (standard of care) or via HMP using the LLT System.

Subjects will have a pre-procedure physical examination and pre-procedure clinical laboratory tests on the day of the liver transplant. Additionally, all subjects will have pre-procedure vital signs collected, including body temperature.

The date and time of donor cross-clamp will be recorded, as well as the estimated liver weight. The types and volumes of flush solutions used prior to, during, and following preservation via

static cold storage or HMP with the LLT System will be recorded. Additionally the type and volume of cold storage preservation solution and the volume and lot number(s) of Vasosol® used for HMP with the LLT system will be documented. The ischemic and total perfusion times will be recorded.

For livers undergoing HMP, the liver will be cannulated, prepared, and placed in the LLT100 System for perfusion by appropriately trained and qualified members of the transplant team, as identified by each site's lead investigator. The date and time at which the additives are mixed with Vasosol® will be recorded, the start and stop time for adding oxygen to Vasosol and oxygen flow rate will be recorded, as well as perfusion start and stop dates and times. HMP flow settings, hepatic artery and portal vein flow rates and pressures, as well as perfusate temperature, will be documented at five minutes, one, two and three hours after initiation of HMP and terminally (immediately prior to liver removal from the LLT System). Perfusate temperature will also be collected at the start of perfusion. The lot/serial numbers of the investigational devices will be recorded. One 6 mL perfusate sample of Vasosol® will be obtained from the sample port of the LLT System for future analysis at the beginning of HMP, as close to and no less than one hour after initiation of HMP and at least one hour before termination of perfusion, and terminally (immediately prior to liver removal from the LLT System).

For livers undergoing static CS, one 6 mL aliquot of preservation fluid surrounding the CS liver will be obtained at termination of preservation, prior to removal of the liver from the bag, and stored for future analysis.

Post-preservation, a needle biopsy of the donor liver will be performed for RNA*later*™ storage.

Liver transplantation will be performed using standard techniques. Immediately prior to transplantation, grafts in both groups will be flushed via the portal vein to wash out residual perfusion/storage solution; the type of solution used and amount used [mL] will be recorded. Needle biopsies of the donor liver for RNA*later*™ and formalin storage will be performed at a minimum of 60 minutes post-arterial reperfusion during the transplant procedure, prior to abdominal closure, for analysis by a central, independent pathologist.

Standard post-operative care will occur for all subjects according to site procedures. Included in the post-operative care is the monitoring of fluids and electrolytes and maintaining the patency of drainage tubes. Vital signs will be monitored and subjects will be assessed for any adverse events (AEs) that may have occurred.

Liver Transplant/Visit 1 Tasks and Data Collection

- Randomization (pre-procedure) of the recipient to liver preservation via static cold storage (control) or HMP using the LLT System (treatment) will occur after initial acceptance by the transplant team for the recipient. Stratified randomization will be performed by lab MELD-Na score determined at time of organ offer, based on UNOS allocation labs and DCD liver type to balance the treatment and control groups as follows:
  - Model for End Stage Liver Disease (MELD)-Na score (lab MELD): ≤30 or >30; and
  - Liver donation after cardiac death (DCD): Yes or No.

  Each randomized subject will receive a unique randomization number, with randomization performed utilizing the built-in randomization feature of the EDC system.

- Physical exam (*pre-procedure*) will include height, weight, BMI (auto calculated) and assessments of general appearance and skin/dermatological, neurological, cardiovascular, respiratory, gastrointestinal, and genitourinary systems.
- Clinical laboratory tests (*pre-procedure)*:
  - *Pre-procedure* chemistry data to be collected include sodium, potassium, chloride, bicarbonate, BUN, SCr, AST, ALT, Total Bili, calculated GFR, alkaline phosphatase, total protein: albumin/globulin ratio (calculated). Renal function (post-procedure) will be assessed through calculated GFR, serum creatinine and urinary output.
  - *Pre-procedure* hematology data to be collected include WBC, ANC, HGB, HCT and platelets.
  - *Pre-procedure* coagulation data to be collected include PT and INR.
- Clinical laboratory tests (*post-procedure)*:
  - *Every 6 hours post-reperfusion for first 24 hours* samples will be collected for measuring SCr, AST, ALT, TBili and INR.
  - *At 3, 6, 12 and 24 hours after reperfusion* arterial lactate will be collected
- Vital signs (*pre-procedure and 0.5, 1, and 2 hours post-procedure*)
  Vital signs will include body temperature, heart rate, systolic and diastolic blood pressures, mean arterial blood pressure (auto calculated), and respiratory rate.
- Preservation Data and Parameters
  Data collection will include donor surgeon(s), preservationist(s) and affiliation, donor hospital, location of donor hospital, warm dissection time (incision-cross clamp), cross-clamp date and time, estimated liver weight, variant anatomy, lot/serial numbers for the LLT100, LLT CART, LLT200 Perfusion Circuit(s), LLT300 Sterile Drape(s), LLT400 Oxygenation Lid Set, liver cannula and connector set (if used), flush solution types (e.g., University of Wisconsin [UW] Solution [SPS-1, BELGen, Belzer's UW], histidine-tryptophan-ketoglutarate [HTK], other) and volumes (mL), static cold storage solution type (e.g., University of Wisconsin [UW] Solution [SPS-1, BELGen, Belzer's UW], histidine-tryptophan-ketoglutarate [HTK], other) and volume (mL), Vasosol® lot number, volume (L) and date and time of mixing additives for livers undergoing HMP with the LLT System, start and stop time for adding oxygen to Vasosol solution and oxygen flow rate for livers undergoing HMP, end-of-preservation flush solution type and volume (mL) (prior to transplant), time of extubation and time of asystole for DCD livers, ischemic times (warm ischemic time [WIT] defined as time from extubation to time of initiation of cold flush for DCD livers, total cold ischemic time (CIT) defined as cross-clamp time to reperfusion time), total HMP (perfusion) time (including perfusion start and stop dates and times), pre-perfusion CS and post-perfusion CS (as applicable), HMP flow setting, perfusion log data including Hepatic Artery (HA) and Portal Vein (PV) flow rates and pressures at 5 minutes, 1 hour, 2 hours, 3 hours, and terminally (immediately prior to liver removal from the LLT System). Perfusate temperature will also be recorded at the start of HMP (time zero), and at five minutes, one hour, two hours, and three hours after initiation of perfusion, and terminally (immediately prior to liver removal from the LLT System). For livers undergoing HMP, one 6 mL sample of perfusate will be obtained from the sample port of the LLT System at each of the following three time points: at the beginning of perfusion; as close to and no less than one hour after initiation of perfusion and at least one hour prior to termination of perfusion; and at termination of perfusion (immediately prior to liver removal from the LLT System). For livers undergoing static CS, one 6 mL aliquot of preservation fluid surrounding the CS liver will be obtained at termination of preservation, prior to removal of the liver from the bag. These samples are to be placed on ice for

transport to be retained for future analysis (e.g., determination of levels of LDH, ALT and AST)..

- Post-preservation donor liver biopsy
  A needle biopsy for RNA*later*™ storage will be performed for potential (optional) analysis by a central, independent pathologist to determine the levels of standard enzyme markers for injury.
- Liver transplant procedure
  Data collection will include date of hospital admission, date of liver transplant, surgeon(s), assistant(s), total operative time including operative start and stop dates and times, time and date of reperfusion, blood products transfused (including packed red blood cells [PRBCs], fresh frozen plasma [FFP] and platelets, autologous blood transfusion/cell saver blood [if applicable]), donor arterial anatomy (e.g., normal, right hepatic artery [RHA] from superior mesenteric artery [SMA], left hepatic artery [LHA] from left gastric artery [LGA], RHA from SMA and LHA from LGA, other), anatomical reconstruction (arterial, venous, biliary, other), intraoperative bile production, urine output, ascites, primary closure (yes/no), intraoperative instability and significant events.
- Post-reperfusion donor liver biopsy
  Needle biopsies of the donor liver for RNA*later*™ and formalin storage will be performed at a minimum of 60 minutes after arterial reperfusion during the transplant procedure, prior to abdominal closure, for analysis by a central, independent pathologist. Samples stored in RNA*later*™ may undergo analysis for further assessment (optional) to determine the levels of standard enzyme markers for injury. The following will be documented:

  - Macrovesicular Steatosis
    - 0-10% (mild)
    - 11-20% (mild)
    - 21-30% (mild)
    - 31-40% (moderate)
    - 41-50% (moderate)
    - 51-60% (moderate)
    - > 60% (severe)
  - Ischemic Injury (severity/ type)
    - Absent
    - Present
      - Coagulative necrosis
      - Mild (single necrotic hepatocytes)
      - Moderate (small groups of necrotic hepatocytes)
      - Severe (large area of necrotic hepatocytes)
  - Cholestasis
    - None
    - Mild
    - Moderate
    - Severe
  - Central Fibrosis
    - Absent
    - Present
      - Sinusoidal (“chicken wire”)
      - Perivenular
  - Batts-Ludwig Classification

Staging of Chronic Hepatitis (single score from 0 to 4)

Staging Terminology		
Semi-quantitative	**Descriptive**	**Criteria**
0	No fibrosis	Normal connective tissue
1	Portal fibrosis	Fibrosis portal expansion
2	Periportal fibrosis	Periportal or rare portal-portal septa
3	Septal fibrosis	Fibrous septa with architectural distortion; no obvious cirrhosis
4	Cirrhosis	Cirrhosis

Grading of Disease Activity in Chronic Hepatitis (single score from 0 to 4)

Grading Terminology		Criteria	
Semi-quantitative	**Descriptive**	**Lymphocytic piecemeal necrosis**	**Lobular inflammation and necrosis**
0	Portal inflammation only; no activity	None	None
1	Minimal	Minimal; patchy	Minimal; occasional spotty necrosis
2	Mild	Mild; involving some or all portal tracts	Mild; little hepatocellular damage
3	Moderate	Moderate; involving all portal tracts	Moderate; with noticeable hepatocellular change
4	Severe	Severe; may have bridging fibrosis	Severe; with prominent diffuse hepatocellular damage

- Suzuki Assessment Score: A score of 0 to 4 will be assigned for each of the following: sinusoidal congestion, cytoplasmic vacuolization (ballooning degeneration), and hepatic necrosis; total score will range from 0 to 12.

Suzuki Score (total score from 0 to 12)

Score	Sinusoidal Congestion	Cytoplasmic Vacuolization	Hepatic Necrosis
0	None	None	None
1	Minimal	Minimal	Single Cell Necrosis
2	Mild	Mild	<30%
3	Moderate	Moderate	≤60%
4	Severe	Severe	>60%

- Post-transplant chest x-ray and Doppler ultrasound
  Post-transplant, chest x-ray and Doppler ultrasound imaging will be performed.
- Biliary complications
  The presence of biliary complications, including stricture or leaks, and whether re-intervention or re-operation was required will be documented. If biliary complications require intervention, the event will be further classified as to type (intrahepatic or extrahepatic, anastomosis-related, ischemic or non-ischemic), type of intervention, whether magnetic resonance cholangiopancreatography (MRCP) performed, and if so, associated findings.
- Vascular complications
  The presence or absence of vascular complications, including hepatic artery thrombosis, portal vein thrombosis, and vascular injury will be documented.
- Graft failure
  The presence or absence of graft failure will be documented.
- Monitor for adverse events
  Adverse events will be assessed from initiation of HMP or static cold storage of the liver through six months post-transplant, death, or study withdrawal, whichever occurs first. Radiographic studies and Doppler ultrasounds will be completed according to standard of care and as medically indicated.

13.6.3 Visits 2-8 (Post-Transplant Days 1-7)

Assessments on Visits 2 through 8 will be identical. If a subject is discharged from the hospital prior to Post-Transplant Day 7, then the subject will be instructed to return to the site for the Day 7 visit. (*Note:* If the subject is discharged prior to Post-Transplant Day 7 and unable to return for Day 7 visit, labs drawn ±2 days of Day 7 may be used). Otherwise, Visits 2-8 will occur while the subject is still admitted in the hospital.

Vital signs, including body temperature, will be monitored daily. Only one set of vital signs is required on each of these visits, although the site may collect multiple sets per standard post-op monitoring procedures. A physical exam will be conducted in order to monitor general well-being as well as to monitor for liver-related complications. Blood draws will also be performed at each of these daily visits for clinical laboratory tests.

Radiographic studies and post-op monitoring will be completed, per the site's standard of care protocols. Subjects will also be assessed for any adverse events (AEs) that have occurred.

Visits 2-8 Tasks and Data Collection

- Subject Status
  The subjects status indicating whether the subject was alive and hospitalized, alive and discharged from the hospital, withdrawn from the study or deceased will be documented.
- Length of required ICU care
  The date of ICU clearance or orders for ICU transfer will be captured and the number of days the subject required ICU care will then be auto-calculated based on the date of transplant and the date of transfer out of the ICU, or the date ICU clearance or orders for ICU transfer were written.
- Initial hospital discharge
  If the initial hospital discharge has occurred the date of discharge will be captured. The time from transplant to hospital discharge [days] will be calculated. The discharge location of the subject will be documented (e.g., rehabilitation center, home, other).
- Hospital readmission (if applicable)
  If hospital readmission occurs, the date of hospital readmission, name of hospital or facility, primary reason for readmission, and date of discharge will be documented.
- Physical exam (*once daily*) will include height, weight, BMI and assessments of general appearance and skin/dermatological, neurological, cardiovascular, respiratory, gastrointestinal, and genitourinary systems.
- Clinical laboratory tests (*Post-transplant Days 1 – 7 while hospitalized*):
  - Chemistry data to be collected include sodium, potassium, chloride, bicarbonate, BUN, SCr, calculated GFR, AST, ALT, alkaline phosphatase, TBili, total protein: albumin/globulin ratio (calculated) and lactate once daily post-transplant while hospitalized up to 7 days post-transplant or discharge, whichever occurs first. Renal function will be assessed through calculated GFR, serum creatinine and urinary output. Twelve hour and 24 hour cumulative urine output (0001-1200 and 1201-2400) will be documented while hospitalized up to 7 days post-transplant while hospitalized.
  - Hematology data to be collected include WBC, ANC, HGB, HCT and platelets once daily post-transplant while hospitalized up to 7 days post-transplant or discharge, whichever occurs first.
  - Coagulation data to be collected include PT and INR once daily post-transplant while hospitalized up to 7 days post-transplant or discharge, whichever occurs first.
  - If AST $\geq$ 3000 blood gas samples for measuring arterial and/or venous pH will be obtained to assess for PNF.
- Vital signs (*once daily*)
  Vital signs will include body temperature, heart rate, systolic and diastolic blood pressures, mean arterial blood pressure (auto calculated), and respiration rate.
- Standard of care radiographic studies, Doppler ultrasounds and post-operative monitoring
  If standard of care radiographic studies and/or Doppler ultrasounds were completed, the type of testing, the date testing was completed and a summary of the key findings of these studies will be documented.
- Early allograft dysfunction (EAD)
  The presence or absence of EAD will be documented. If present, the findings will be documented (TBili $\geq$10 mg/dL at seven days post-transplant, INR $\geq$1.6 at seven days post-transplant, and/or AST or ALT >2000 IU/L within seven days post-transplant)

- Primary non-function (PNF)
  The presence or absence of PNF will be documented. If present, the findings will be documented (relisted for orthotopic liver transplant within seven days post-transplant or death within seven days post-transplant without identification of cause such as surgical complications, hepatic artery thrombosis, portal vein thrombosis, or acute rejection, and same blood draw taken 24 hours to 7 days after transplant showing AST ≥ 3000 and one or both of the following: INR ≥ 2.5 or acidosis, defined as having arterial pH ≤ 7.30 or venous pH ≤ 7.25 and/or lactate ≥ 4mMol/L).
- Graft failure
  The presence or absence of graft failure will be documented.
- Biliary complications
  The presence of biliary complications, including stricture or leaks and whether re-intervention or re-operation was required will be documented. If biliary complications require intervention, the event will be further classified as to type (intrahepatic or extrahepatic, anastomosis-related, ischemic or non-ischemic), type of intervention, method of confirmation of biliary complications (if any) including whether MRCP performed, and if so, associated findings.
- Vascular complications
  The presence or absence of vascular complications, including hepatic artery thrombosis, portal vein thrombosis, and vascular injury resulting in disruption of blood flow will be documented.
- Renal Dysfunction: AKI
  The presence or absence of AKI based on RIFLE criteria (≥ 2X SCr from baseline or decrease in GFR by > 50%; or urine output < 0.5 mL/kg/hr for ≥ 12 hours) within seven days post-transplant will be documented. Twelve (12) and 24 hour cumulative intake and output will be documented daily while hospitalized up to seven days post-transplant.
- Monitor for adverse events
  Adverse events will be assessed from initiation of HMP or static cold storage of the liver through six months post-transplant, death, or study withdrawal, whichever occurs first.

13.6.4 Visits 9 and 10 (3 Months ± 7 Days Post-Transplant; 6 ± 1 Month Post-Transplant))

Assessments on Visits 9 and 10 will be identical. Visit 9 will occur at three months post-transplant ± 7 Days and Visit 10 will occur at six months post-transplant ± 1 month. The site will record the necessary hospital discharge information as indicated in the eCRFs, if this information was not captured at a previous visit. Subjects will be questioned about any adverse events that have occurred since the previous visit. The following lists provides the entire set of tasks that will be addressed at this visit:

Visits 9 and 10 Tasks and Data Collection

- Subject Status
  The subjects status indicating whether the subject was alive and hospitalized, alive and discharged from the hospital, withdrawn from the study or deceased will be documented.
- Initial hospital discharge
  If not captured during previous visit, the date of the initial hospital discharge and discharge location of the subject will be documented (e.g., rehabilitation center, home, other). The time from transplant to initial hospital discharge [days] will be calculated.
- Hospital readmission (if applicable)

If hospital readmission occurs, the date of hospital readmission, name of hospital or facility, primary reason for readmission, and date of discharge will be documented.

- Physical exam will include height, weight, BMI (auto calculated), and assessments of general appearance and skin/dermatological, neurological, cardiovascular, respiratory, gastrointestinal, and genitourinary systems.
- Clinical laboratory tests will include the following:
  - Chemistry data including sodium, potassium, chloride, bicarbonate, BUN, SCr, calculated GFR, AST, ALT, alkaline phosphatase, TBili, total protein: albumin/globulin ratio (calculated) and lactate will be collected. Renal function will be assessed through calculated GFR and serum creatinine.
  - Hematology data including WBC, ANC, HGB, HCT and platelets will be collected.
  - Coagulation data including PT and INR will be collected.
- Vital signs
  Vital signs will include body temperature, heart rate, systolic and diastolic blood pressures, mean arterial blood pressure (auto calculated), and respiratory rate.
- Standard of care radiographic studies, Doppler ultrasounds and post-operative monitoring
  If standard of care radiographic studies and/or Doppler ultrasounds were completed, the type of testing, the date testing was completed and a summary of the key findings of these studies will be documented.
- Graft failure
  The presence or absence of graft failure will be documented.
- Biliary complications
  The presence of biliary complications, including stricture or leaks and whether re-intervention or re-operation was required will be documented. If biliary complications require intervention, the event will be further classified as to type (intrahepatic or extrahepatic, anastomosis-related, ischemic or non-ischemic), type of intervention, method of confirmation of biliary complications (if any) including whether MRCP performed, and if so, associated findings.
- Vascular complications
  The presence or absence of vascular complications, including hepatic artery thrombosis, portal vein thrombosis, and vascular injury resulting in the disruption of blood flow will be documented.
- Monitor for adverse events
  Adverse events will be assessed from initiation of HMP or static cold storage of the liver through six months post-transplant, death, or study withdrawal, whichever occurs first.

13.6.5 Visit 11 (12 ± 1 Month Post-Transplant)

Visit 11 will consist of documentation of the subject and graft status at 12 months post-transplant ± 1 month.

Visit 11 Tasks and Data Collection

The 12 month outcome assessment will include:

- Date of visit or documentation of subject status
- Subject Status
  Subject status (e.g., alive, withdrawn from the study or deceased) will be documented.
- Graft Failure Assessment
  The presence or absence of graft failure will documented (e.g., dysfunction, failure, re-transplanted or re-listed for transplantation).

13.6.6 Early Termination Visit

A subject may terminate early from the study for multiple reasons. The site will complete the tasks noted below.

Early Termination Visit Tasks and Data Collection

- Date of Early Termination Visit

The date of the early termination visit will be documented.
The following data will be collected to the extent possible if early termination occurs between study visits:

- Subject Status
  The subject's status indicating whether the subject was alive and hospitalized, alive and discharged from the hospital, withdrawn from the study or deceased will be documented.
- Length of required ICU care
  The date of ICU clearance or orders for ICU transfer will be captured and the number of days the subject was in the ICU or required ICU care will then be auto-calculated based on the date of transplant and the date of transfer out of the ICU, or the date ICU clearance or orders for ICU transfer were written.
- Initial hospital discharge
  If not captured during previous visit, the date of the initial hospital discharge and discharge location of the subject (e.g., rehabilitation center, home, other) will be documented. The time from transplant to hospital discharge [days] will be calculated.
- Hospital readmission (if applicable)
  If hospital readmission occurs, the date of the hospital readmission, name of hospital or facility, primary reason for readmission, and date of discharge will be documented.
- Physical exam will include height, weight, BMI (auto calculated), and assessments of general appearance, and skin/dermatological, neurological, cardiovascular, respiratory, gastrointestinal, and genitourinary systems.
- Clinical laboratory tests will include the following:
  - Chemistry data including sodium, potassium, chloride, bicarbonate, BUN, SCr, calculated GFR, AST, ALT, alkaline phosphatase, TBili, total protein: albumin/globulin ratio (calculated) and lactate will be collected. Renal function will be assessed through calculated GFR and serum creatinine.
  - Hematology data including WBC, ANC, HGB, HCT and platelets will be collected.
  - Coagulation data including PT and INR will be collected.
- Vital signs
  Vital signs will include body temperature, heart rate, systolic and diastolic blood pressures, mean arterial blood pressure (auto calculated), and respiratory rate.
- Standard of care radiographic studies, Doppler ultrasounds and post-operative monitoring
  If standard of care radiographic studies and/or Doppler ultrasounds were completed, the type of testing, the date testing was completed and a summary of the key findings of these studies will be documented.
- Early allograft dysfunction (EAD)
  The presence or absence of EAD will be documented. If present, the findings will be documented (TBili $\geq$ 10 mg/dL at seven days post-transplant, INR $\geq$ 1.6 at seven days post-transplant, and/or AST or ALT > 2000 IU/L within seven days post-transplant).
- Primary non-function (PNF)

The presence or absence of PNF will be documented. If present, the findings will be documented (relisted for orthotopic liver transplant within seven days post-transplant or death within seven days post-transplant without identification of cause such as surgical complications, hepatic artery thrombosis, portal vein thrombosis, or acute rejection, and same blood draw taken 24 hours to 7 days after transplant showing AST ≥ 3000 and one or both of the following: INR ≥ 2.5 or acidosis, defined as having arterial pH ≤ 7.30 or venous pH ≤ 7.25 and/or lactate ≥ 4mMol/L).

- Graft failure
  The presence or absence of graft failure will be documented.
- Biliary complications
  The presence of biliary complications, including stricture or leaks and whether re-intervention or re-operation was required will be documented. If biliary complications require intervention, the event will be further classified as to type (intrahepatic or extrahepatic, anastomosis-related, ischemic or non-ischemic), type of intervention, method of confirmation of biliary complications (if any) including whether MRCP performed, and if so, associated findings.
- Vascular complications
  The presence or absence of vascular complications, including hepatic artery thrombosis, portal vein thrombosis, and vascular injury will be documented.
- Renal Dysfunction: AKI
  The presence or absence of AKI based on RIFLE criteria (≥ 2X SCr from baseline or decrease in GFR by > 50%; or urine output < 0.5 mL/kg/hr for ≥ 12 hours) within seven days post-transplant will be documented. Twelve (12) and 24 hour cumulative intake and output will be documented daily while hospitalized up to seven days post-transplant.
- Monitor for adverse events
  Adverse events will be assessed from initiation of HMP or static cold storage of the liver through six months post-transplant, death, or study withdrawal, whichever occurs first.

13.6.7 Subject Study Completion

The outcome of each subject will be documented. Data collection will include the date of study completion, status of the subject (e.g., alive, deceased or withdrawn from study) and graft function at the time of study completion (e.g., function, dysfunction, failure, re-listed for transplant or re-transplanted). If the patient is deceased, the primary cause of death (if known), whether or not an autopsy was performed and whether or not the death was associated with an AE will be captured.

14.0 PRIMARY SAFETY AND EFFECTIVENESS OUTCOMES

The primary safety and effectiveness endpoint is EAD (early allograft dysfunction), which is defined as the presence of one or more of the following: total bilirubin ≥ 10 mg/dL at seven days post-transplant; INR ≥ 1.6 at seven days post-transplant; or AST or ALT > 2000 IU/L within seven days of transplant.[4]

15.0 ADDITIONAL OUTCOMES

15.1 Secondary Safety and Effectiveness

The secondary safety and effectiveness endpoints of this study are the following:

1. PNF (primary non-function) defined as relisted for orthotopic liver transplant within seven days of transplant or leading to death within seven days of transplant without identification of cause such as surgical complications, hepatic artery thrombosis, portal vein thrombosis, or acute rejection, and same blood draw taken 24 hours to seven days after transplant showing:
   - AST ≥ 3000 and one or both of the following:
     - INR ≥ 2.5 or
     - Acidosis, defined as having arterial pH ≤ 7 .30 or venous pH ≤ 7.25 and/or lactate ≥ 4mMol/L
2. Peak AST, ALT, INR, SCr, and TBili (every 6 hours for initial 24 hours, daily thereafter) within seven days post-transplant or discharge, whichever occurs earlier.
3. Acute kidney injury (AKI) based on RIFLE criteria (≥ 2X SCr from baseline or decrease in Glomerular filtration rate (GFR) by > 50%; or Urine output < 0.5 mL/kg/hr for ≥ 12 hours) within seven days of transplant.
4. Incidence within 3 months and 6 months post-transplant of any of the following:
   - Graft failure
   - Biliary complications
   - Vascular complications
   - Subject death

15.2 Exploratory

Exploratory endpoints of this study are the following:

1. Lactate clearance: arterial lactate 3, 6, 12, 24 hours after reperfusion
2. Time to normality defined as: AST (12–38 IU/mL), ALT (7–41 IU/mL), TBili (0.3–1.3 mg/dL), SCr (0.6–1.12 mg/dL) and INR (0.87–1.16)
3. Time from transplant to hospital discharge [days]
4. Graft failure at 12 months
5. Subject death at 12 months

16.0 STATISTICAL ANALYSIS AND PLANNED ANALYSIS

16.1 Introduction

This study is a prospective, randomized, controlled study comparing hypothermic machine perfusion (HMP) of explanted livers using the LLT System with Vasosol® with control livers preserved via static cold storage (standard of care). The study will be conducted at up to eight centers in the U.S. A study center is defined as a hospital under the control and supervision of the Principal Investigator. Subjects will be enrolled in the trial for a period of twelve months. The objectives of the statistical analyses are to evaluate safety and effectiveness of the LLT System with Vasosol® in the preservation of explanted livers.

16.2 Sample Size and Power

The study is sized with respect to the primary effectiveness endpoint of the study, which is the incidence of Early Allograft Dysfunction (EAD). Expected incidences of EAD for the test arm and the control arm are assumed to be 15% and 30%, respectively, based on published results and previous experience with a prototype system, as follows.[1,2,4-6]

A prototype of the LLT System with Vasosol® to perform HMP was evaluated in 20 patients as compared to matched control patients receiving a liver preserved via static cold storage.[1] The study included use of standard criteria donor (SCD) livers and extended criteria donor (ECD) livers, with a similar number of SCD and ECD livers in both groups (6 SCD livers and 14 EDC livers in HMP group, and 7 SCD livers and 13 EDC livers in the control group). Published outcomes stated EAD rates of 5% in the HMP group versus 25% in the control group.

Another study evaluating the prototype of the LLT System with Vasosol® in 31 patients as compared to matched control patients receiving a liver preserved via static cold storage was conducted that included only ECD livers.[2] EAD rates were 19% in the HMP group versus 30% in the control group.

Others have reported incidences of EAD for livers having undergone static cold storage at 23%,[4] 40%,[5] and 18% (for liver donation after brain death) to 45% (for liver donation after circulatory death).[6]

In summary, studies using the prototype LLT System with Vasosol® resulted in EAD rates of 5% to 19% versus EAD rates in the matched control groups of 25% to 30%. EAD rates in other studies of livers having undergone static cold storage have been reported to range up to 45%, with dependent factors including the health status of recipient and the quality of the donor liver. The present study allows inclusion of higher risk recipients (*i.e.*, ≥18 years of age, high MELD-Na scores), as well as use of marginal donor livers (*i.e.*, DCD, declined by local/regional centers, Donor Risk Index ≥ 1.6, elevated liver function tests, donor having undergone CPR). Therefore, the incidences of EAD in the present study are expected to be similar to those reported in the second study using the LLT System prototype as compared to control (19% and 30%, respectively). Specifically, for the present study, the EAD rate for livers undergoing HMP with the LLT System with Vasosol® is expected to be slightly improved at 15% because the study is not limited to use of extended criteria donor livers. The EAD rate for livers undergoing static cold storage is conservatively estimated at 30%,

given the 30% incidence observed in the previous study and the reported EAD rates of up to 45% in other studies.

Therefore, based on the statistical analysis and acceptance criterion, and an estimated attrition rate of 10%, a sample size of 70 subjects per study arm is sufficient to demonstrate non-inferiority at 80% power with a non-inferiority margin δ of 7.5% using a frequentist approach.

16.3 Analysis Populations

The following analysis populations will be defined for the study:

Intent to Treat (ITT) Population – The ITT population will consist of all subjects who have signed informed consent, been enrolled in the study, randomized, and the assigned liver preservation method has been initiated.

Per Protocol (PP) Population - The PP population will consist of all subjects in the ITT population who have completed a liver transplant procedure and completed the primary efficacy evaluations according to the procedures outlined in this protocol and do not have any protocol deviations outlined in the protocol (*i.e.*, study eligibility criteria not met, lack of informed consent, error in study group assignment, error in conduct of the trial, subject management or subject assessment).

Safety Population – The safety population will consist of all subjects in the ITT population who have an attempted liver transplant procedure, regardless of whether the transplant was successful.

The analysis population for the primary efficacy analysis will be the ITT and PP populations. The analysis population for baseline and demographic analyses, and secondary safety and effectiveness and exploratory outcomes will be the safety population.

16.4 Subgroup Analyses

There are no subgroup analyses planned for the study.

16.5 Statistical and Analytical Plans

16.5.1 Analysis of Demographics and Baseline Characteristics

Summary statistics for all demographic and baseline variables for the test and control arms will be provided to demonstrate that subjects enrolled in this study are representative of the Intended Use population. This analysis will be performed on the safety population, the ITT and the PP populations and provided overall by study arm.

16.5.2 Primary Safety and Effectiveness Analyses

The incidence rates of EAD between the test arm using the LLT System and the control arm will be compared to demonstrate that EAD incidence is within a clinically reasonable margin. Specifically, the following hypothesis is being tested:

$$H_0: \mathrm{EAD}_{LLT} - \mathrm{EAD}_{Control} > \delta \text{ vs. } H_a: \mathrm{EAD}_{LLT} - \mathrm{EAD}_{Control} \leq \delta,$$

where EAD indicates EAD incidence rate and δ is the non-inferiority margin. The hypothesis will be tested by evaluating whether the upper limit of the one-sided 95% confidence interval for the difference in incidence rates is smaller than or equal to δ. A non-interiority margin δ of 7.5% will be considered as a clinically relevant margin to show non-inferiority.

Point estimates and 95% confidence intervals (CIs) for incidence rates will be provided by study arm along with point estimates and 95% CIs for differences in incidence rates between the study arms.

This analysis will be performed on the ITT population, and repeated for the PP population.

16.5.3 Secondary Safety and Effectiveness Analyses

For all binary outcomes, point estimates and 95% CIs for incidence rates will be provided by study arm along with point estimates and 95% CIs for differences in incidence rates between the study arms. For continuous outcomes, point estimates and 95% CIs for Least Squares means (LS means) will be provided by study arm along with point estimates and 95% CIs for differences in LS means between the study arms. This analysis will be performed on the Safety population.

A detailed description of all statistical methods will be provided in a separate SAP that will be finalized prior to database lock.

16.5.4 Additional Safety Analysis

Prior to analysis, unanticipated AEs not defined in protocol ("other" AEs) will be coded using the MedDRA coding dictionary. Based on these coded terms, AEs will be summarized using system organ class and preferred terms, as well as by relationship to the LLT System. This analysis will be performed on the Safety population.

Additional safety analyses may be performed as described in the SAP for the study.

16.6 Handling Missing Data

For handling missing data, multiple imputation methods will be used to impute and address effects of any missing data. The analysis methods for missing data will be pre-specified and described in the SAP for the study.

16.7 Interim Analysis

There are no interim analyses planned for this study.

17.0 ANTICIPATED ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Equipment, supplies, and properly skilled personnel must be available to treat any unexpected event.

17.1 Definitions

Anticipated AEs

An **Anticipated AE** is one that is described in the labeling, in the instructions for use, in the protocol, in the consent form and in peer reviewed literature, including any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (e.g., abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

The **Anticipated AEs** and supporting data will be recorded in accordance with the list of Anticipated AE terms and definitions outlined below in **Table 17.1** that reflect the known risks associated with the LLT System with Vasosol® and liver transplantation.

Table 17.1 – Anticipated AE Terms and Definitions

ANTICIPATED AE TERMS AND DEFINITIONS		
#	**AE Term**	**AE Definition**
1.	**Severe Preservation Injury**	Severe preservation injury is defined as peak aspartate aminotransferase (AST) > 5000 U/L within the first 72 hours post-transplant, in the absence of vascular thrombosis, biliary obstruction, sepsis or reversible cause of shock**.**
2.	**Primary Non-Function (PNF)**	PNF is defined as re-listed for orthotopic liver transplant within seven days of transplant or leading to death within seven days of transplant without identification of cause such as surgical complications, hepatic artery thrombosis, portal vein thrombosis, or acute rejection, and laboratory data from the same blood draw taken 24 hours to seven days post-transplant showing: a. AST ≥ 3000 and one or both of the following: (1) INR ≥ 2.5 or (2) Acidosis, defined as having arterial pH ≤ 7.30 or venous pH ≤ 7.25 and/or lactate ≥ 4mMol/L
3.	**Early Allograft Dysfunction (EAD)**	EAD is defined as the presence of one or more of the following: a. Total bilirubin ≥10 mg/dL at seven days post-transplant b. International normalized ratio (INR) ≥ 1.6 at seven days post-transplant c. Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) >2000 IU/L within seven days of transplant.
4.	**Graft Rejection**	Graft rejection is defined as destruction of the transplanted organ by the recipient's immune system. Graft rejection is determined based on presence of strong clinical evidence of rejection requiring treatment and/or confirmed by liver biopsy. If liver biopsy results are available, graft rejection will be sub-categorized as follows: a. **Acute Cellular Rejection:** Occurs days to years post transplantation. Characterized histologically by mixed portal inflammation consisting of lymphocytes, eosinophils, neutrophils, and plasma cells, lymphocytic cholangitis, portal venule or central vein endotheliitis. Acute cellular rejection will be graded according to the Banff scheme (0-9 points with 3 being the minimum score to definitively diagnose acute cellular rejection). b. **Chronic Graft Rejection:** Occurring more than 6 months post-transplant, characterized by bile duct loss in at least 50% of the portal tracts, dysmorphia

ANTICIPATED AE TERMS AND DEFINITIONS		
#	**AE Term**	**AE Definition**
		of residual ducts, and arteriopathy (in cases in which medium caliber arteries are present to evaluate). Centrilobular cholestasis, centrilobular hepatocyte swelling, and scattered apoptotic bodies may be present. May present in conjunction with acute cellular rejection. c. **Humoral Rejection (Antibody Mediated Rejection [AMR]):** a form of allograft injury and subsequent dysfunction that is primarily mediated by antibody and complement, occurring immediately (hyperacute) or later (acute) after transplant, and may be associated with the recipient's pre-existing antibodies against the graft or represent anti-donor antibodies that develop after transplant. The antigen-antibody complex activates the complement system, resulting in massive thrombosis in the capillaries that prevents the vascularization of the graft. Later manifestations may present mainly with injury to endothelial cells and require C4d immunohistochemistry. Diagnosis shortly post-transplant requires that conditions such as preservation injury, hepatic artery or portal vein thrombosis, or venous outflow obstruction can be excluded with reasonable certainty. Associated findings may include consumptive coagulopathy and operative site bleeding requiring the administration of blood products. May present in conjunction with acute cellular rejection.
5.	**Graft Failure**	Graft failure is defined as clinical loss of function of the transplanted liver. Symptoms of graft failure may include elevation in liver function tests (AST, ALT, and TBili), ascites and mental status changes.
6.	**Ischemic Injury**	The presence and degree of ischemic injury will be assessed through liver biopsy findings post-reperfusion as follows: a. Coagulative necrosis b. Mild (single necrotic hepatocytes) c. Moderate (small groups of necrotic hepatocytes) d. Severe (large area of necrotic hepatocytes)
7.	**Vascular Injury and Complications**	Vascular injury and/or complications of the arterial and/or venous blood vessels following liver transplant resulting in disruption of blood flow. Vascular injuries and complications will be categorized as follows: a. **Hepatic Artery Thrombosis**: Obstruction of the arteries in the liver caused by blood clot formation in the hepatic artery. b. **Portal Vein Thrombosis:** A form of venous thrombosis affecting the hepatic portal vein which can lead to portal hypertension and reduction in the blood supply to the liver. c. **Vascular Injury**: Liver vascular injury related to cannulation of liver vessels for perfusion.
8.	**Major Bleeding**	Post-operative bleeding requiring surgical re-intervention, excessive post-biopsy bleeding (beyond what is normally anticipated) requiring transfusion of packed red blood cells (PRBCs), the development of a hematoma at the liver biopsy site requiring intervention, and/or other type of significant bleeding that required intervention or transfusion.
9.	**Biliary Complications**	Subject presentation may be asymptomatic with elevated cholestatic liver enzymes or may exhibit abdominal pain, jaundice, fever, increased liver enzymes and recurrent cholangitis. Biliary complications will be confirmed as needed by liver ultrasound, Doppler imaging, computed tomography angiography, endoscopic retrograde cholangiopancreatography (ERCP), or MRCP . ***Categorization of Biliary Complications*** Biliary complications will be categorized with respect to type, and whether intervention or re-operation is required. a. **Biliary Strictures:** A biliary stricture is an abnormal narrowing of a portion of the biliary tree. b. **Biliary Leaks:** A biliary leak is a hole in the bile-duct system that causes bile to spill into the abdominal cavity that persists beyond post-operative day 3, is

ANTICIPATED AE TERMS AND DEFINITIONS		
#	**AE Term**	**AE Definition**
		confirmed by cholangiography or contrast enhanced ultrasound, and/or requires intervention such as ERCP, additional drainage or re-operation. If intervention is required, the event will be further categorized as follows: **a. Intrahepatic:** Intrahepatic biliary complications occur or originate within the liver. **b. Extrahepatic:** Extrahepatic biliary complications occur or originate outside the liver. **c. Anastomotic Biliary Complications:** Anastomotic biliary complications occur at the site of the duct to duct anastomosis and are typically isolated and shorter in length. **Non-anastomotic Biliary Complications:** Non-anastomotic complications usually occur in the hilar region but may occur diffusely in the recipient biliary tract. Non-anastomotic strictures are related to ischemic and /or immune injury to the biliary mucosa during liver transplant d. **Ischemic:** Biliary complications resulting from ischemic/reperfusion induced tissue injury or other root causes associated with ischemia. (e.g. prolonged cold ischemic time, hepatic artery thrombosis or ABO blood group incompatibility) **e. Non-ischemic:** Biliary complications resulting from non-ischemic root causes (*e.g.*, hepatic artery obstruction)
10.	**Renal Dysfunction**	Renal Dysfunction will be subcategorized as acute kidney injury (AKI) or chronic kidney disease (CKD) based on the following criteria. a. **AKI** defined by RIFLE criteria is characterized within seven days of transplant: (1) An acute significant reduction in the glomerular filtration rate (GFR) >50% from baseline, (2) An increase in serum creatinine (SCr) ≥ 2 times from baseline, or (3) Urinary output < 0.5 mL/kg/hr for ≥ 12 hours. b. **CKD** defined by National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) Guidelines is either: (1) kidney damage (abnormal renal pathologies or markers for ≥ 3 months, with or without decreased GFR); or (2) GFR <60 mL/min/1.73 m^2 for ≥ 3 months with or without kidney damage. Classification includes: (1) Stage 1 kidney damage with GFR ≥90 ml/min/1.73 m^2; (2) Stage 2 kidney damage with GFR 60-89 ml/min/1.73 m^2; (3) Stage 3 GFR 30-59 ml/min/1.73 m^2; (4) Stage 4 GFR 15-29 ml/min/1.73 m^2; and (5) Stage 5 ESRD, dialysis or GFR ≤15 ml/min/1.73 m^2.
11.	**Infection**	A clinical infection accompanied by symptoms including pain, fever, drainage and/or leukocytosis that is treated by anti-microbial agents (non-prophylactic). A positive culture from the infected site or organ should be present unless strong clinical evidence indicates the need for treatment despite negative cultures. Infections will be subcategorized as follows: a. **Localized Infection:** Infection localized to any organ or region (e.g. *peritonitis or urinary tract infection*) without evidence of systemic involvement, ascertained by standard clinical methods and either associated with evidence of bacterial, viral, fungal or protozoal infection and/or requiring empirical treatment. b. **Abdominal Abscess:** A pocket of infected fluid and pus that is surrounded by inflamed tissue located inside the abdominal cavity. c. **Sepsis or Systemic Inflammatory Response (SIR):** Evidence of systemic involvement by infection, manifested by positive blood cultures and/or hypotension.

ANTICIPATED AE TERMS AND DEFINITIONS		
#	**AE Term**	**AE Definition**
12.	**Elevated Portal Pressures**	Portal hypertension (PH) represents an increase of the hydrostatic pressure within the portal vein or its tributaries. It is defined as an increase in the pressure gradient between the portal vein and hepatic veins or the inferior vena cava (IVC).
13.	**Cholestasis**	Cholestasis is an impairment of the flow of bile from the liver and/or bile ducts to the duodenum. Causes of cholestasis will be subcategorized as follows: a. Ischemia/reperfusion injury b. Rejection of the transplanted liver c. Sepsis/Serious infection d. Intrahepatic biliary strictures e. Hepatic artery thrombosis f. Drug hepatotoxicity g. Recurrent liver disease
14.	**Thrombocytopenia**	Thrombocytopenia is defined as blood disease characterized by an abnormally low number of platelets (<150,000 per mcL) in the bloodstream.
15.	**Incisional Hernia**	An incisional hernia is a protrusion of the tissues of the abdomen through the weakened abdominal muscles caused by the incision or an incompletely-healed surgical wound.
16.	**Other**	An anticipated AE with a known association with the disease process and/or liver transplantation that was not included in the list of Anticipated AE Terms and Definitions in the Clinical Protocol.

A ***serious adverse event (SAE)*** is defined as an adverse event that:

1. Led to death
2. Led to serious deterioration in the health of the subject, that either resulted in:
   a. a life-threatening illness or injury, or
   b. a permanent impairment of a body structure or a body function, or
   c. in-patient or prolonged hospitalization, or
   d. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function

The seriousness and severity must be evaluated independently when documenting the AEs on the eCRF.

A ***life threatening adverse event*** is any AE that places the subject at immediate risk of death from the event as it occurred. A life-threatening event does not include an event that might have caused death had it occurred in a more severe form but that did not create an immediate risk of death as it actually occurred.

Hospitalization is to be considered only as an overnight (or longer) admission. Hospitalization or prolongation of a hospitalization is a criterion for considering an AE to be categorized as serious. In the absence of an AE, the participating Investigator should not report hospitalization or prolongation of hospitalization on a form.

In addition, a hospitalization planned before the start of the study for a preexisting condition that has not worsened does not constitute an SAE (e.g., elective hospitalization immediately after the procedure was performed and before study completion).

An ***unanticipated adverse device effect (UADE)*** is a serious adverse effect caused by or associated with the device which was not previously identified in nature, severity or degree of

incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

17.2 Reporting of Serious Adverse Events

This section will address the reporting of the SAE to Organ Recovery Systems.

In the event that any SAEs occur during this study, the Investigator or designated study personnel will notify Organ Recovery Systems or the CRA (Clinical Research Associate) assigned to their site via email (PILOT-Safety@precisionformedicine.com) or phone <CRA phone number> immediately (within 24 hours) after becoming aware of the incident.

The Investigator will provide SAE source documentation regarding the SAE to Organ Recovery Systems or the CRA. The Investigator will promptly provide follow-up information requested by Organ Recovery Systems or their CRA. All SAEs will be followed until resolution or the Investigator judges the event to be chronic or stable.

Organ Recovery Systems will report all adverse events that are serious, unexpected, and considered at least possibly related to the device to the FDA, IRBs, and participating investigators within 10 working days after first receiving notice of the event.

17.3 Collecting, Recording and Reporting Adverse Events

Adverse events will be recorded from the time of initiation of HMP or static cold storage of the liver through six months post-transplant, death, or study withdrawal, whichever occurs first. The Investigator is responsible for ensuring that all AEs are observed and reported during the study on the corresponding page of the AE eCRF.

The Investigator will determine when AEs occur at all stages of subject evaluation during the study. AEs will be recorded stating the duration (i.e., onset and resolved dates) of the event, the intensity (mild, moderate, severe), seriousness, the relationship to the device (‘yes’ [definitely, probably, possibly], or ‘no’ [not related]) action taken (none, medication, surgical intervention, other), and the outcome (fatal, not recovered/not resolved, recovered/resolved, recovered/resolved with sequelae, recovering/resolving, unknown). It will be noted whether or not the AE resulted in the subject’s withdrawal from participation in the study.

The Investigators must use appropriate medical terminology and concepts when the AEs are recorded on the eCRF and avoid jargon and abbreviations.

Note: The AE must be recorded on the AE page of the eCRF. Each AE should be marked appropriately on the AE page as to whether it is serious. An SAE and any UADE must be reported to the Sponsor or the designated safety personnel as soon as possible (within 24 hours). FDA regulations require Investigators to report any UADE to the Sponsor and IRB no later than 10 days after the Investigator has become aware of its occurrence.

The causal relation between an AE and the study device will be determined by the Investigator on the basis of his or her clinical judgment and the following definitions:

- ***Definitely related:*** Event can be fully explained by use of the investigational device.

- ***Probably related***: Event is most likely to be explained by use of the investigational device rather than the subject's clinical state or other agents/therapies.
- ***Possibly related***: Event may be explained by use of the investigational device or by the subject's clinical state or other agents/therapies.
- ***Not related***: Event can be fully explained by the subject's clinical state or other agents/therapies.

When assessing the relationship between the investigational device and an AE, the following should be considered:

1. Temporal relationship between the use of the investigational device and the AE
2. Biological plausibility of relationship
3. Subject's underlying clinical state
4. When applicable, whether the AE abates on discontinuation of the use of the investigational device

SAEs that are not study related may nevertheless be considered by the participating Investigator or the Medical Monitor (or designee) to be related to the conduct of the clinical study, i.e., to a subject's participation in the study. For example, a protocol-related SAE may be an event that is related to another non-test procedure required by the protocol.

The following definitions should be used when determining the severity or intensity of an AE:

- ***Mild:*** The AE is noticeable to the subject but does not interfere with routine activity.
- ***Moderate:*** The AE interferes with routine activity but responds to symptomatic therapy or rest.
- ***Severe:*** The AE significantly limits or prevents the subject's ability to perform routine activities despite symptomatic therapy.

17.4 AE Outcome Assessment

AEs will be followed until recovery/resolution or six months post-transplant, death or study withdrawal, whichever occurs first.

17.5 Reporting Device Malfunctions

A device malfunction denotes a malfunction, failure or inability of the LLT System with Vasosol® to perform its intended function, which will be documented in the eCRF. If a Device Malfunction impacts the health of a person (subject, user or other) during the study, it is also considered an AE and recorded as such.

The data collected include: the date of the device malfunction; the time of the malfunction (if known); the name of the person recording the device malfunction; the location where the device malfunction occurred (e.g., procurement site, during transit, transplant site or other location); the LLT System with Vasosol® component that failed; the root cause and precipitating factors of the device malfunction; whether perfusion ceased and if so, duration and perfusion parameters prior to cessation and upon re-initiation of perfusion; the effect on liver preservation; whether liver was utilized; and whether the device malfunction resulted in an AE.

18.0 STUDY SUSPENSION, TERMINATION, AND COMPLETION

The Sponsor may suspend or terminate the study or part of the study at any time for any reason. If the Investigator suspends or terminates the study, the Investigator will promptly inform the Sponsor and the IRB and provide them with a detailed written explanation.

18.1 Termination by the Sponsor / Stopping Rules

The Sponsor may terminate the study, or the study site, at any time for any of the following reasons:

1. Failure to enroll subjects
2. Protocol violations
3. Inaccurate or incomplete data
4. Unsafe or unethical practices
5. Questionable safety of the investigational device, including occurrence of UADEs.
6. Suspected lack of appropriateness of the investigational device
7. Administrative decision

18.2 Termination by the Investigator

If the Investigator terminates the study prematurely, the Investigator must do the following:

1. Return all study devices and related study materials to the Sponsor.
2. Provide the IRB and the Sponsor with a written statement describing why the study was terminated prematurely. Prompt compliance with this requirement is essential so that the Sponsor may comply with its regulatory obligations.

18.3 Study Completion

Upon study completion, the Investigator will provide the Sponsor, IRB, and regulatory agency with final reports and summaries as required by regulations. The Investigator must submit a written report to the Sponsor and the IRB within three months after the completion or termination of the study. Study termination and follow-up will be performed in compliance with the Sponsor's or designee's standard procedures.

19.0 PROTOCOL AMENDMENTS

An Investigator must not make any changes to the study without prior approval by the Sponsor except when necessary to eliminate apparent immediate hazards to the subjects, as described in **Section 20**.

Prior approval by the FDA and reviewing IRB are also required for any protocol change that may affect the scientific soundness of the investigation, or the rights, safety, or welfare of the subjects.

20.0 PROTOCOL DEVIATIONS

Protocol deviations, including those related to study eligibility criteria, informed consent, study group assignment, conduct of the trial, subject management or subject assessment shall be documented. The Investigator shall notify the Sponsor and reviewing IRB of any protocol deviation to protect the life or physical well-being of a subject in an emergency as soon as possible, and in no event later than 5 working days after the emergency occurred.

21.0 QUALITY CONTROL AND ASSURANCE

The Sponsor will perform quality control and quality assurance checks on this clinical study in accordance with regulatory agency data integrity requirements and data management SOPs. Before enrolling any subjects in the study, the clinical study monitor and the Investigator(s) will review the protocol, the eCRF instructions, the procedure for obtaining informed consent and the procedure for reporting AEs and SAEs.

A qualified representative of the Sponsor will monitor the conduct of the study by visiting the site, by contacting the site by telephone, and sending emails. During the visits, information recorded on the eCRFs will be verified against source documents. The Sponsor's Medical Monitor or designee reviews the data for safety information. The Sponsor's clinical data associates or designees review the data for legibility, completeness, and logical consistency.

Additionally, the Sponsor's clinical data associates or designees use automated validation programs to help identify missing data, selected protocol violations, out-of-range data, and other data inconsistencies. Access to the database shall be limited to appropriate personnel, per 21 CFR 11 compliance.

22.0 DIRECT ACCESS, DATA HANDLING, AND RECORD-KEEPING

22.1 Investigator

The Investigator will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to original source data and documents. All subject information will be recorded on source documents. The eCRFs must be fully completed and include all required data for all subjects enrolled. All eCRF data must be submitted to the Sponsor throughout and at the end of the study.

22.2 Data Handling

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the Site Principal Investigator. All data will be collected on source documentation and source document verification (SDV) will be conducted to ensure data collected are reliable and allow reconstruction and evaluation of the study. The Investigator must provide direct access to the source documents to Organ Recovery Systems, the CRO, or its representative. An eCRF will be completed for every subject who signs a written ICF and is enrolled into the study.

Data for this study will be entered and accepted from the site into a 21 CFR 11 Compliant Electronic Data Capture (EDC) system. The Clinical Research Coordinator shall complete the eCRF by adding or updating subject information. Once data has been entered, the Monitor shall view the eCRFs and verify the data with the source documents. In the SDV process, information reported by the Investigator is compared with the original records to ensure that it is complete, accurate, and valid. Throughout the course of the study data management shall also review the data. This review will ensure that missing, out-of-range, or incomplete data is queried and resolved.

A database lock will occur once all data has been entered, SDV is completed, all queries resolved, quality assurance procedures have been completed, and the data has been deemed clean.

Specific instructions for data management and programming procedures will be detailed in an overall Data Management Plan (DMP).

22.3 Data Queries

The Monitor shall perform source document verification of all data points. Discrepancies and data errors will be reconciled with the Clinical Research Coordinator or designated study personnel. The EDC will track the revisions and the reason why the revision occurred will be documented. Queries will be generated as needed for reconciliation of data errors and discrepancies discovered in their review of source documents during and/or following the monitoring visit. When queries are necessary, the Monitor will select the appropriate field and generate an electronic query. Upon notification, the Clinical Research Coordinator will respond with a reason for the discrepancy and document that data is correct as documented or will provide a corrected resolution to the data field. The Monitor shall review the resolution and close the query, if appropriate. If additional information is required the Monitor will continue the process until all data requirements are satisfied.

Queries will also be generated by data management, for mistakes and discrepancies encountered during data review and through logic checks. When queries are necessary, the data manager will select the appropriate field and generate the electronic query. Upon notification, the Clinical Research Coordinator will respond with a reason for discrepancy and document that data is correct as documented or will provide a corrected resolution to the data field. The data manager shall review the query resolution and close the query when appropriate. If further information is required for resolution to the query, the data manager will initiate the process until all data requirements are satisfied.

22.3.1 Study Site Personnel Changes

If an Investigator retires, relocates, or otherwise withdraws from conducting the study, the Investigator must notify the Sponsor to agree upon an acceptable Investigator replacement and corresponding study personnel. Regulatory agencies will be notified with the appropriate documentation of personnel change.

Study personnel logs, with designated responsibilities, will be updated accordingly.

22.3.2 Adverse Event Reporting

The Investigator agrees to report all AEs to the Sponsor as described in **Section 17.2**. Furthermore, the Investigator is responsible for ensuring that any Co-Investigator or Sub-Investigator promptly brings AEs to the attention of the Investigator. The Investigator also is responsible for informing the sponsor and participating IRB of any UADEs.

22.3.3 Review of Source Records

Source documents will be maintained on site and will consist of but not be limited to: progress notes, completed Sponsor provided template source documents.

The Investigator agrees that qualified representatives of the Sponsor and regulatory agencies will have the right, both during and after this study, to conduct inspections and to audit and review medical records pertinent to the clinical study as permitted by the regulations. Subjects will not be identified by name, and confidentiality of information in medical records will be preserved. The confidentiality of the subject will be maintained unless disclosure is required by regulations. Accordingly, and in compliance with 21 CFR 50.25(c), the following statements (or similar statement) will be included in the informed consent document:

> "Your individually identifiable information from this study will be used and disclosed as described in the form entitled "Authorization to Use and Disclose Protected Health Information" that you will be asked to sign."

> "This clinical trial will be registered on *http://www.ClinicalTrials.gov,* as required by U.S. Law. This web site will not include information that can identify you. The web site may include a summary of the results when the study is completed. You can search this web site at any time."

22.4 Security/Storage of Data

The EDC product being used for this study is in compliance with 21 CFR 11, electronic records, electronic signatures and predicate rules. Compliance is achieved through a combination of SOP adherence and a structured validation system.

Security of the EDC system includes the use of passwords that limit user access according to their job responsibilities. Access to the data at the clinical site is restricted to authorized personnel only. Usernames and passwords are sent in two separate emails to personalized email addresses only.

The Investigator shall retain and preserve copies of all data generated in the course of the study, specifically including but not limited to those documents defined by GCP as essential documents, for the longer of: (1) two years after the last marketing authorization for the study device has been approved or the Sponsor has discontinued its research with respect to such device; or (2) such longer period as required by applicable global regulatory requirements. At the end of such period, the Investigator shall notify the Sponsor of the intent to destroy all such material. The Sponsor shall have 30 days to respond to the Investigator's notice, and the Sponsor shall have a further opportunity to retain such materials at the Sponsor's expense.

22.4.1 Monitoring of the Study

This study is monitored by a representative of the Sponsor. Site visits are made before the study begins, at regular intervals during the study, and at the study closeout. Communication by telephone and mail and e-mail may be used as needed to supplement site visits. The Investigator and study site will permit monitoring, audits, IRB review, and regulatory inspection by providing authorized personnel from the Sponsor, its representatives, the IRB, the FDA and other appropriate regulatory agency direct access to all study data. Any party with direct access will take reasonable precautions to maintain the confidentiality of the study subjects and Organ Recovery Systems' proprietary information. The purpose of the site visits is to verify the following:

1. Adherence to the protocol. The Investigator shall document and explain any deviation from the approved protocol.
2. The completeness and accuracy of the eCRFs. Adequate time and space for these visits should be allocated by the investigator.
3. Compliance with regulations. The verification will require comparison of the source documents to the eCRFs.
4. All subject records have complete, accurate and plausible ICFs and all study-specific logs.

22.5 Data Extract

Data will be extracted from the EDC system into SAS datasets for analysis and submission to the Regulatory Authorities.

23.0 SUBJECT INJURY

In general, subject to specific provisions in the clinical trial agreement, if a subject is injured as a direct result of an investigational device product, the Sponsor will pay for reasonable and necessary medical treatment for the injury, to the extent that such expenses are not covered by the subject's medical insurance, a government program, or other responsible third party.

If laws or regulations of the locality in which the study is taking place require additional payment of expenses, the Sponsor shall comply with such laws or regulations. Where applicable, the Sponsor has purchased clinical trial insurance that is applicable nationwide.

24.0 CONTROL AND ACCOUNTABILITY OF INVESTIGATIONAL PRODUCT

The Investigator shall ensure that the investigational device will only be used for subjects who are participating in this study. The Investigator will not provide the device or any of its components to any person who is not authorized to receive it.

Upon completion of the study, all remaining test products will be accounted for and returned to the Sponsor under separate cover via a traceable method (UPS, FedEx, etc.) or as otherwise instructed by the Sponsor.

The Sponsor will maintain a log of all investigational supplies shipped or supplied, and the investigational site will maintain a log of all supplies used and/or returned to the Sponsor.

25.0 PUBLICATIONS POLICY

The Sponsor will be responsible for determining when the study results should be published. Results on all pre-specified outcomes will be provided through, and in accordance with, the designated requirements of *ClinicalTrials.gov* no later than one year after the final completion date of the study, including the release of outcomes if the outcomes are negative or the study is terminated early. Study results may also be published in peer-reviewed medical journals. The Sponsor will work jointly with the investigators to publish information. The Investigator shall not submit a publication to journals or professional societies without agreement and prior written approval of the Sponsor.

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