Evaluating the Safety of Utilizing Donor Hearts from Donation after Circulatory Death (DCD) Donors compared to Donor Hearts from Donation after Brain Death (DBD) Donors: A Single Center Pilot

National Clinical Trial (NCT) Identified Number: NCT05462041

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Funded by: Cedars Sinai Medical Center

Version Number: v.2.0

04 Aug 2022

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form, recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Evaluating the Safety of Utilizing Donor Hearts from Donation after Circulatory Death (DCD) Donors compared to Donor Hearts from Donation after Brain Death (DBD) Donors: A Single Center Pilot Study.
Study Description:	The purpose the research is to evaluate whether patients who receive a Donation after Circulatory Death (DCD) heart for cardiac transplantation using either normothermic regional perfusion (NRP) or direct procurement and perfusion (DPP) have similar outcomes as patients who receive Donation after Brain Death (DBD) heart using standard cold storage. The study will also evaluate whether DCD procured hearts have a meaningful impact on hearts available for transplantation at our center.
Objectives:	The primary objective of this proposed research is to evaluate the safety of utilizing DCD donor hearts as compared to DBD donor hearts for transplantation. The secondary objective is to assess the practical, financial, and logistical viability of using NRP vs. DPP for the procurement of DCD donor hearts.
Endpoints:	Primary Endpoints: Incidence of heart graft-related Serious Adverse Events (HGRSAEs) in the first 30 days post-heart transplantation in the DCD Heart Transplanted Recipient Population, defined as the following adverse events (at most one per type): • Moderate or Severe heart PGD (left or right ventricle) (not including rejection or cardiac tamponade) • Primary graft failure requiring retransplantation • Patient and graft survival at 30 days post-transplant

- Patient and graft survival at 30 days and initial hospital discharge, if later than 30 days
- Use of post-transplant mechanical circulatory support (ECMO, LVAD, RVAD, BiVAD) for > 72 hours immediately post-transplant.

Secondary Endpoints:

- Length of time on waiting list for DCD hearts (compared to time on waiting list for DBD heart for that patient, and compared to the median time for a patient matched for height and ABO group)
- Utilization rates of heart offers, donors attended, and hearts explanted in DCD donors as compared to DBD donors.
- Cost per DCD transplant and cost saving per DCD transplant (especially for in-patients/MCS patients)

Study Population:	Study subjects will be drawn from patients listed for heart transplant at Cedars-Sinai Medical Center.
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	This study is designed to be conducted as a single-center prospective pilot trial at Cedars Sinai Medical Center in Los Angeles, California.
Description of Study Intervention:	The primary research procedures are procurement and utilization of DCD donor hearts for transplantation and data collection/analysis.
Study Duration:	The total study duration is 18 months.
Participant Duration:	The study includes 7 research visits. Total subject participation is 30 Days

1.2 SCHEDULE OF ACTIVITIES (SOA)

Procedures /Assessments	**Screening Visit**	**Visit #1 (Day 0 at Transplant)**	**Visit #2 (Day 7 post-transplant ± 2 days)**	**Visit #3 (Day 14 post-transplant ± 2 days)**	**Visit #4 (Day 21 post-transplant ± 2 days)**	**Visit #5 (at hospital discharge)**	**Visit #6 (Day 30 post-transplant ± 7 days)**
Eligibility & Informed Consent	X						
Demographics/Characteristics	X						
Medical & Cardiac History	X						
Data Collection Donor Characteristics		X					
Patient Visit (recipient)	X	X	X	X	X	X	X
Heart Transplantation		X					
Data Collection Transplant Details		X					
Data Collection PGD Scores		X	X				X
Data Collection Inotrope Support		X	X			X	X
Right Heart Catheter Data		X					
Data Collection Mechanical Circulatory Support		X	X			X	X
Data Collection Invasive Ventilator Support		X	X				
Endomyocardial Biopsy (recipient)			X	X	X		X
Data Collection Patient Survival							X
Data Collection Graft Survival							X
Data Collection Post-Transplant Hemodynamics		X	X	X	X		X
Data Collection Immunosuppressive Meds & Induction (if applicable)		X	X	X	X	X	X
Data Collection ICU & Hospital Stay						X	
Data Collection Heart Graft-Related AEs and SAEs		X	X	X	X	X	X
Heart Transportation NRP/OCS[1]		X					

[1] DCD donor heart recipients only

2 INTRODUCTION

2.1 STUDY RATIONALE

Heart transplantation remains the gold standard treatment for patients with end-stage heart failure. However, the shortage of suitable donor hearts is a major limitation to the widespread utilization of this life-saving procedure. The most recent report from the Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients reported a 42.5% increase in the number of newly listed heart transplantation candidates from 2008 to 2019. Unfortunately, the number of heart transplantations performed annually has remained steady over the past several years at 3000 to 4000.

Until recently, beating hearts from donation after brain death (DBD) donors were the only heart donors used for transplantation worldwide. The simple preservation method of cold storage became routinely used to transport DBD hearts between the donor and recipient hospitals and adequately preserves these ideal donor hearts. However, during the last 20 years, the number of suitable DBD donors has plateaued while the number of patients diagnosed with end stage organ failure continues to increase. As a result, the waiting list for organ transplantation has grown.

With the increasing number of waitlisted patients, aggressive efforts to expand the donor pool of quality organs are necessary. The disparity between the supply of and demand for donor hearts has led to renewed interest in donation after circulatory death (DCD) in heart transplantation. Studies have estimated that DCD heart transplantation can increase the availability of donor hearts by up to 30%.

2.2 BACKGROUND

Normothermic Regional Perfusion (NRP)

Although DCD transplantation has been performed for other organs in the United States, programs for DCD heart transplantation have yet to be fully established. A primary concern is irreversible myocardial injury and organ damage from warm ischemia time (WIT) and reperfusion injury, to which the heart is particularly vulnerable given its high-energy requirements.

Recent studies from DCD heart transplantation programs in the United Kingdom (UK) and Australia have reported 30-day and 1-year survival, graft function, and incidence of rejection comparable to those with conventional donation after brain death (DBD) heart transplant recipients. Despite these encouraging results, the UK and Australian DCD approaches using ex situ perfusion devices have limitations in terms of cost and concern for primary graft dysfunction (PGD) necessitating extracorporeal membrane oxygenation (ECMO).

To mitigate these factors, we propose a DCD heart transplantation protocol using cardiopulmonary bypass (CPB) for normothermic regional perfusion (NRP) based on established strategies for NRP DCD donor heart retrieval. The proposed benefits of this strategy include optimal myocardial protection, correction of metabolic abnormalities associated with circulatory arrest, and in situ functional assessment of the donor organ prior to transplant.

Direct Procurement and Perfusion (DPP) utilizing the Organ Care System (OCS)

For the past several decades there has been scientific and clinical interest in the development of ex-vivo heart perfusion (EVHP) with oxygenated and nutrient enriched blood to reduce ischemic injury to the donor heart and potentially enable ex-vivo assessment of metabolic and mechanical function. More recently, EVHP has been used to potentially expand the donor pool to include hearts from donation after circulatory death (DCD).

However, due to potential damage of warm ischemia in the donor and the functional arrest of the heart that may never recover, DCD donors are not widely utilized for adult heart transplantation in the U.S. In contrast, international transplant centers have been successfully transplanting hearts from DCD donors, using the OCS Heart System for resuscitation, preservation and assessment of these hearts prior to transplantation. The OCS Heart System can minimize the detrimental effects of ischemia because it perfuses the donor heart with warm oxygenated blood. It enables the heart to be resuscitated to full beating state, and importantly enables the transplant team to assess metabolic (lactate production) and perfusion parameters of these hearts to determine their suitability for transplantation.

Currently, the TransMedics' OCS Heart technology is the only portable system available for ex-vivo maintenance of the donor heart in a metabolically active and beating state. It is currently FDA approved for the procurement and transport of both DCD and DBD donor hearts.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The main immediate potential risk to study participants is primary graft dysfunction (PGD). A DCD heart suffers a variable warm ischemic injury, circulatory stasis and imperfect subsequent (post-procurement) functional assessment which might increase this risk compared to a standard DBD heart transplant. However, DCD hearts do not suffer the catecholamine storm-induced injury of brain death and are typically procured from younger donors with less potential for so-existing conditions. The early results of several large series of DCD heart transplantation have been reported, and the PGD risk has not been any different from that for DBD heart transplantation. The operative risk of standard DBD heart transplantation varies according to recipient and donor factors, but is typically in the range of 5-10%. A similar risk has been observed in multiple reports of DCD transplantation performed in numerous different centers. Most of these centers have been new to the procedure.

As far as long-term risks, studies have reported follow-up to 5 years which is equivalent to standard heart transplantation. There is no data beyond this, and so no comment regarding the potential for a different rate of coronary vasculopathy can be made, however, there is no signal of this from the medium-term series.

2.3.2 KNOWN POTENTIAL BENEFITS

The potential benefits to the patients are of an earlier heart transplant with a better-quality donor heart. Access to DCD heart transplants is one of the most effective ways of increasing the donor pool for any patient. This applies as much to urgent status patients who are at high priority for a standard donor heart, as it does to low status patients who typically have very long waits for suitable donor organs. Patients who are of large size, ABO blood group O and with durable LVAD implants suffer particularly long waits for appropriate donor hearts, and are therefore subject to a higher waiting list mortality.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Based on the above, the benefits of using DCD donated hearts to expand the donor pool for cardiac transplantation outweigh the potential risks to trial subjects.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
The primary objective of this proposed research is to evaluate the safety of utilizing DCD donor hearts as compared to DBD donor hearts for transplantation.	Incidence of heart graft-related Serious Adverse Events (HGRSAEs) in the first 30 days post-heart transplantation in the DCD Heart Transplanted Recipient Population, defined as the following adverse events (at most one per type): - Moderate or Severe heart PGD (left or right ventricle) (not including rejection or cardiac tamponade) - Primary graft failure requiring retransplantation - Patient and graft survival at 30 days post-transplant - Patient and graft survival at 30 days and initial hospital discharge, if later than 30 days - Use of post-transplant mechanical circulatory support (ECMO, LVAD,	The primary objective of the study is to evaluate the safety of utilizing DCD donor hearts compared to DBD hearts for transplantation. Therefore, outcomes which evidence the function of the transplanted heart have been selected as primary endpoints. Each of the endpoints listed represents, or could represent, failure of the transplanted heart to adequately support the patient.

	RVAD, BiVAD) for > 72 hours immediately post-transplant.	
Secondary		
The secondary objective is to assess the practical, financial and logistical viability of using NRP vs. DPP for the procurement of DCD donor hearts.	- Length of time on waiting list for DCD hearts (compared to time on waiting list for DBD heart for that patient, and compared to the median time for a patient matched for height and ABO group) - Utilization rates of heart offers, donors attended, and hearts explanted in DCD donors as compared to DBD donors. - Cost per DCD transplant and cost saving per DCD transplant (especially for in-patients/MCS patients)	The secondary objectives of the study concern the feasibility of the technique to usefully augment the number of patients to whom we can offer heart transplantation. Therefore, outcomes which evidence the use of resources required for each additional transplant have been selected as secondary endpoints. By bringing forward patients' transplants, DCD heart transplantation may also reduce overall costs for heart transplant patients and therefore this endpoint is also considered. These outcomes will also be used to set the budget going forward.

4 STUDY DESIGN

4.1 OVERALL DESIGN

The proposed study will evaluate two strategies for the retrieval of heart from donors after circulatory death (DCD): Normothermic Regional Perfusion and Direct Procurement and Perfusion with the OCS Heart System. Currently, DCD hearts are approved for use for transplantation (outside of a research protocol) in the US by using the Direct Procurement and Perfusion (DPP) with the OCS Heart System.

In the U.S., heart donation occurs after a person has been declared brain dead and is called a donor after brain death (DBD). In these patients, the heart continues to beat and pump blood throughout the body. After life support is withdrawn, organs are retrieved immediately for transplantation. This study will use hearts from donors after circulatory death (DCD) donors. DCD donors are those whose hearts have stopped beating and no longer pump blood. DCD hearts are not used as often for transplantation

today in the U.S. because they may be further injured during traditional cold storage. In the US, donor hearts are currently mostly obtained from donors after brain death (DBD), although DCD donors are used for other donated organs, such as: lungs, kidneys, and livers.

This study will evaluate whether patients who receive a DCD heart transplant using either NRP or DPP have similar outcomes as patients who receive DBD hearts using standard cold storage. The study will also evaluate whether DCD procured hearts have a meaningful impact on hearts available for transplantation at our center. Ten (10) DCD donor heart recipients will be enrolled into the study intervention group, and approximately 30 DBD donor heart recipients will be enrolled into the control group.

The primary objective of this proposed research is to evaluate the safety of utilizing DCD donor hearts as compared to DBD donor hearts for transplantation. The secondary objective is to assess the practical, financial and logistical viability of using NRP vs. DPP for the procurement of DCD donor hearts.

In order to assess the secondary objective, a total of 8 (± 1) DCD hearts will be procured utilizing NRP and 2 (± 1) DCD hearts will be procured with DPP. Should the NRP target number of eight be met prior to reaching the enrollment goal of 10 DCD donor heart recipients, DPP methods will be utilized for the remaining two DCD heart transplants, as clinically feasible.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study is designed to evaluate the local implementation of a novel (to this institution) technique of donor heart procurement. The scientific and clinical value of DCD heart transplantation has already been established in several large series from expert centers and is accepted in consensus statements from the main societies representing heart transplantation. Therefore, a relatively small number of patients will be recruited, with limited statistical power, common in such a “learning curve” analysis.

4.3 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.2.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

Donor Heart Screening
Donor hearts will be screened for eligibility based on current standard of care criteria.

5.1 DCD DONOR WITH NRP ELIGIBILITY CRITERIA

DCD Donor with NRP Inclusion Criteria

1. Age 18-45 years
2. Weight ≥ 50Kg
3. TTE showing good cardiac function (LVEF ≥ 50%)
4. If there are risk factors for coronary artery disease a coronary angiogram may be requested and if not performed this should be factored into the acceptability of the organ

DCD Donor with NRP Exclusion Criteria

NRP Donor hearts will not be selected if they meet any of the following criteria:

1. Prior chest surgery
2. Cardiac Disease on TTE or on coronary angiogram
3. NRP contraindicated or not supported by donor hospital

5.2 DCD DONOR WITH DPP ELIGIBILITY CRITERIA

DCD Donor with DPP Inclusion Criteria

1. Age 18-45
2. Weight ≥ 50Kg
3. TTE showing good cardiac function (LVEF ≥ 50%)
4. If there are risk factors for coronary artery disease a coronary angiogram may be requested and if not performed this should be factored into the acceptability of the organ (coronary arteries should then be assessed later by direct visualization and palpation of the OCS)

DCD Donor with DPP Exclusion Criteria

DPP Donor hearts will not be selected if they meet any of the following criteria:

1. Prior chest surgery
2. Cardiac Disease on TTE or on coronary angiogram

5.3 DBD DONOR ELIGIBILITY CRITERIA

DBD donor hearts will be screened and determined to be eligible for transplant according to the standard of care of the institution. DBD donor hearts that are eligible for transplantation will be procured using standard cold storage.

5.4 RECIPIENT ELIGIBILITY CRITERIA

Recipient Inclusion Criteria

To be eligible to participate in this study, an individual must meet all the following criteria:

1. Subjects must be willing and be capable of understanding the purpose and risks of the study and must sign a statement of informed consent OR consent of a legally authorized representative of a cognitively impaired individual will be obtained before the cognitively impaired individual may be included in research.
2. Signed: 1) written informed consent document and 2) authorization to use and disclose protected health information
3. Male or female, aged 18 years of age or older listed for primary heart transplant

Recipient Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Prior history of cardiac transplantation
2. Multi-organ transplant
3. Current or planned participation in another interventional trial
4. Recipient has any condition that, in the opinion of the Investigator, would make study participation unsafe or would interfere with the objectives of the study

5.5 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study.

When a subject is matched with and accepts any donor heart (either from a DCD Donor or a DBD Donor), the recipient inclusion and exclusion criteria will be re-verified by the study team. If the recipient is no longer eligible for the trial, they will be considered a screen failure and will exit the study. Trial data will not be collected for subjects who are screen failures.

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

- The patient does not meet eligibility criteria at the time of transplant
- The patient becomes unsuitable for transplantation by any technique
- Standard cold storage is not utilized in DBD Donor Heart transportation
- The patient does not receive a heart transplant or is still on the waiting list at the conclusion of this trial

5.6 STRATEGIES FOR RECRUITMENT AND RETENTION

All patients on the heart transplant waiting list at Cedars-Sinai will be identified by trial investigators and screened for trial eligibility. Those patients who initially appear eligible for the trial will have the trial thoroughly explained to them by a trial investigator, be invited to participate, and will be asked to sign an informed consent. Consent of a legally authorized representative of a cognitively impaired individual will be obtained before the cognitively impaired individual may be included in research.

Consented transplant candidates will be eligible to receive DCD donor hearts that have been deemed clinically acceptable for transplantation by the treating transplant clinical team. Patients who consent to this study and receive a heart transplant will subsequently be entered into this study. Subjects who receive a standard of care DBD donor heart transplant will enter the control arm, while those who receive a DCD donor heart will enter the study arm.

All subjects will be patients of the principal investigator and co-investigators, managed as part of the Cedars-Sinai Advanced Heart Failure/Heart Transplant Program. Subjects will be approached in person during clinic visits or upon hospital admission by investigators or study coordinators after confirming eligibility. No advertising will be used for recruitment purposes.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

The study intervention of DCD donor cardiac transplantation will be compared to a control group of standard of care DBD donor heart transplantations. Due to the in-situ functional arrest of the DCD heart, reperfusion of the organ is performed to resuscitate the heart to a full beating state prior to transplantation. In this study, the two different strategies utilized for DCD heart retrieval are established methods of procuring solid organs. Normothermic Regional Perfusion (NRP) procedures will be used to procure all DCD hearts unless contraindicated or prohibited by the donor hospital. In the event the donor hospital does not allow NRP for cardiac organ procurement, or the target number of eight DCD transplants with NRP has been achieved, Direct Procurement and Perfusion (DPP) with the Organ Care System (OCS) should be utilized (for NRP and DPP methods, see Section 8).

Regardless of perfusion strategy, all DCD donor hearts will undergo standard of care functionality assessments and will only be utilized if they are deemed clinically acceptable for transplantation.

6.1.1 NORMOTHERMIC REGIONAL PERFUSION (NRP) DESCRIPTION

The NRP method uses the Affinity CP Centrifugal Blood Pump (AP40) coupled with the CAPIOX FX Advance Oxygenator and Hardshell Reservoir for extracorporeal circulation of the donor heart prior to harvest. This method will utilize:

- Affinity CP Centrifugal Blood Pump (AP40)
- External Drive Motor Model 560A
- Medtronic pump speed controller
- CAPIOX FX25 Advance Oxygenator with Integrated Arterial Filter and Hardshell Reservoir

Description of Major Components

Affinity CP Centrifugal Blood Pump

The Affinity CP Centrifugal Blood Pump is used to pump blood through the extracorporeal bypass circuit for extracorporeal circulatory support for periods appropriate to cardiopulmonary bypass (up to 6 hours). The pump is designed to move blood by centrifugal force generated by a combination of a smooth rating cone and low-profile impeller fins. Energy is transferred from the pump in the form of pressure and velocity as the blood is driven toward the outlet port of the pump. To limit friction and heat generation, the Affinity CP Centrifugal Blood Pump utilizes a pivot-bearing design on a dual ceramic pivot. It has been sterilized using ethylene oxide.

The Affinity CP Centrifugal Blood Pump couples to a remote magnetic drive unit called the External Drive Motor Model 560A, which interfaces with a Medtronic pump speed controller. It also couples with the Emergency Handcrank Model HC150A in the event of controller or power failure. Additional information about the external drive motor and the emergency handcrank is located in the appropriate Medtronic pump speed controller operator's manual.

CAPIOX FX25 Advance Oxygenator and Hardshell Reservoir

The CAPIOX FX is a membrane oxygenator with microporous polypropylene hollow fibers, to be used as an extracorporeal gas exchange device in which the blood flows on the outside of the fibers and with the ventilating gas flowing through the fibers.

The CAPIOX FX consists of:

- A module for gas exchange with an integrated heat exchanger and arterial filter
- Hardshell reservoir with an integrated cardiotomy filter

The integrated heat exchanger is used to warm or cool blood and/or perfusion fluid as it flows through the device. The hardshell reservoir is used to store blood during extra-corporeal circulation from the venous line and the cardiotomy line. The reservoir contains a venous section that is comprised of a filter and defoamer to facilitate air bubble removal. The cardiotomy section of the reservoir contains a filter to remove particulate matter and a defoamer to facilitate air bubble removal.

All blood contacting surfaces are coated with Xcoating Surface Coating, which is a bio-compatible material that is applied on the blood-contacting surfaces of the device to reduce the adhesion of platelets to the device.

Normothermic Regional Perfusion procedures will be conducted per Cedars-Sinai's institutional standard of care.

6.1.2 DIRECT PROCUREMENT AND PERFUSION (DPP) DESCRIPTION

Direct Procurement and Perfusion Description

The DPP method will utilize the Organ Care System (OCS Heart System), which is an integrated portable platform designed to maintain donor hearts in a near physiologic, normothermic perfusion state. The OCS Heart System consists of:

- OCS Heart Console
- OCS Heart Perfusion Set – comprised of Heart Perfusion Module (HPM) and Accessories
- OCS Heart Solution Set

The OCS system is commercially available and approved for use in transportation of donor hearts for cardiac transplantation.

These major components are shown in Figure 1 below.

Figure 1: Figures of the OCS Heart System

Description of Major Components

OCS Heart Console

The OCS Heart Console is the reusable, non-sterile portable enclosure incorporating the electronics, software, fluid pumping systems, monitoring systems, power supply, batteries, gas cylinder, mobile base and Wireless Monitor. The Wireless Monitor displays information and allows the user to adjust certain settings.

The OCS Heart Console provides a rigid compartment to house and securely connect to the HPM during transport. The OCS Heart Console connects to a mobile base with locking wheels.

Heart Perfusion Set (HPS)

The Heart Perfusion Set (HPS) consists of the Heart Perfusion Module (HPM) and Disposable Accessories. The HPM provides a closed circulatory system to protect, maintain and support the heart. It uses a physical conduit to connect to the heart, incorporates various sensors, and interfaces with the OCS Heart Console to oxygenate, warm and circulate the perfusate.

The accessories are intended to:

- Collect and process the donor blood
- Prime and then infuse the OCS Heart Solution to the HPM
- Connect the heart to the HPM circuit
- Facilitate monitoring of the heart operation
- Infuse cardioplegia to terminate the preservation.

The HPM provides the sterile blood circuit and protected environment for a heart within the OCS. It is designed as a single-use, pre-assembled module that mounts into the OCS. The heart is instrumented within the heart chamber of the HPM. The Wireless Monitor displays measurements made within the HPM. The HPM includes:

- Dual lid heart-specific heart chamber
- Integrated and easily accessible blood sampling and de-airing manifold
- Integrated pulsatile pump head interface
- Integrated low shear titanium blood warmer
- Integrated blood oxygenator (or gas exchanger)
- Integrated sensors (pressure and temperature) and circuitry to communicate with the Console.

OCS Heart Solution Set

The OCS Heart Solution Set consists of two proprietary heart preservation solutions, a Priming Solution and a Maintenance Solution, to replenish the nutrients and hormones (adenosine) that the metabolically active donor heart requires. The solutions are packaged in a three-chamber bag (nominal volume of 500 ml per chamber). At the time of use, the Priming Solution (500 ml) is dispensed into the HPM. The Maintenance Solution is manufactured as two component solutions (500 ml each) that are individually manufactured and then mixed immediately before infusion into the HPM. Additives are required at the time of use.

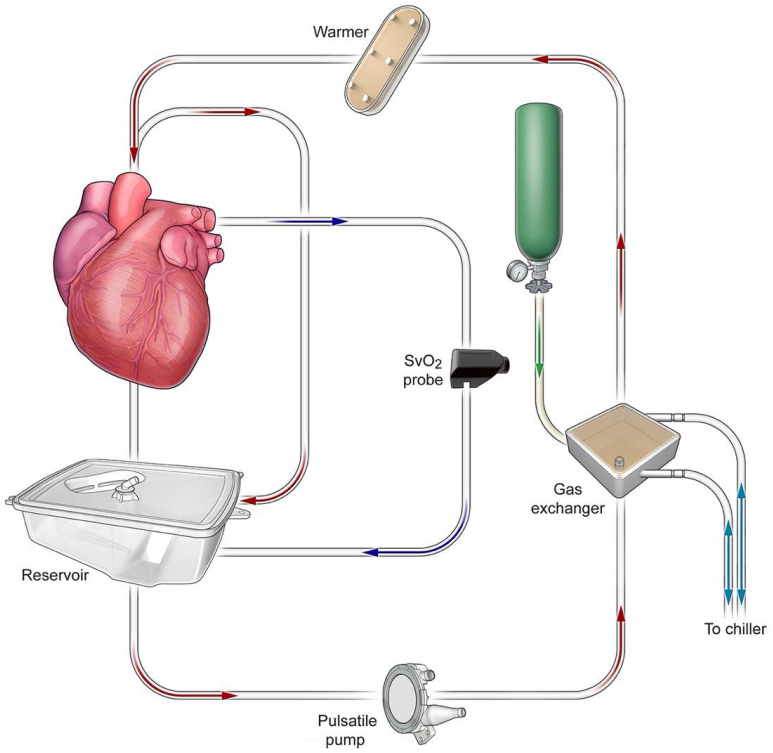
The OCS Heart Solution Set is not intended to be administered directly to the donor or the recipient. The donor heart is arrested prior to removal using a standard cardioplegia solution. Prior to transplantation into the recipient, the donor heart is arrested on the OCS through the use of a standard cardioplegia solution, at which time the perfusate (including the donor blood, Priming Solution and Maintenance Solution) are flushed from the donor heart.

Mode of Action – Overview

The OCS Heart System preserves the heart in a near-physiological, beating state by perfusing the heart with a warmed, donor-blood based perfusate that is supplemented with nutrients and oxygen in a controlled and protected environment referred to as the circuit. The circuit is illustrated in Figure 2 below. The OCS contains a pulsatile pump that directs flow through the gas exchanger, to be

oxygenated, and then through the blood warmer and then to the aorta of the donor heart. An additional perfusate component, known as the Maintenance Solution, is infused into this circuit. The heart consumes oxygen and nutrients as the blood travels from the aorta through the coronary arteries and returns blood to the circuit through its pulmonary artery. The OCS maintains the blood at a constant temperature, oxygenates the perfusate at a constant rate, and provides perfusate in a pulsatile flow at a constant rate.

Figure 2: Schematic of the OCS Heart System Fluid Flow



6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The investigator or designee will maintain a record of OCS Heart System devices received, used, or discarded under this protocol.

All device components and supplies utilized for Normothermic Regional Perfusion will be supplied per standard institutional guidelines.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The Affinity CP Centrifugal Blood Pump and Medtronic External Drive Motor Model 560A are manufactured by Medtronic. The CAPIOX FX Advance Oxygenator with Integrated Arterial Filter and Hardshell Reservoir is manufactured by Terumo. Refer to the appropriate device brochure and instructions for use for additional product information.

The OCS Heart Perfusion Set and accessories and the Perfusion Solution will be supplied sterile and are intended and labeled for single use only. The OCS and its components will be clearly labeled with instructions for use for the device. The OCS Heart System utilized in this protocol is manufactured by TransMedics.

6.2.3 PRODUCT STORAGE AND STABILITY

The Affinity CP Centrifugal Blood Pump should be stored at temperatures between -30°C and 57°C, and ambient humidity from 20-85%, no condensing. Do not store the CAPIOX FX at extreme temperatures and humidity; avoid direct sunlight.

The Organ Care System (OCS) devices will be stored in a secure location. Access should be strictly limited to the investigators and their designees. The OCS Heart Perfusion Set should be stored at temperatures between -20°C and 50°C, and ambient humidity from 10-95%, no condensing.

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

6.2.4 PREPARATION

See Method for NRP (Section 8.2) and Method for DPP (Section 8.3).

6.3 STUDY INTERVENTION COMPLIANCE

Not Applicable.

6.4 CONCOMITANT THERAPY

For this protocol, inotropic medication, immunosuppressive medication and induction therapies will be collected at timepoints specified in the Schedule of Activities (Section 1.2). Inotropic medication doses will be collected at ICU admission T0, T12, T24, T48 and T72 hours after ICU admission post-heart transplantation. In addition, medications used to treat all serious heart graft-related serious adverse events (SAEs) will be recorded.

7 STUDY STOPPING RULES AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 STUDY STOPPING RULES

The criteria below provide guidance for suspending trial enrollment/DCD donor heart utilization until review by the Data and Safety Monitoring Board (DSMB) (Section 10.1.6).

Selected serious adverse events (SAEs) of concern and their thresholds are:

- Two (2) episodes of severe primary graft dysfunction (PGD) per ISHLT grading criteria (left or right ventricle, not including rejection or cardiac tamponade) requiring extracorporeal membrane oxygenation (ECMO) within 24 hours after transplant in subjects who received DCD donors.
- Two (2) deaths occur in subjects who received DCD donors within 7 days after transplant

It is the responsibility of the Principal Investigator to report all of the above SAEs to the DSMB within 24 hours of discovering the event.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Subjects will be considered screen failures if they require a multi-organ transplant or become unsuitable for transplantation by any technique. A subject will be considered enrolled in the study if they undergo a heart transplant (either DCD or DBD) that meets the eligibility criteria as described in Section 5.
Participants are free to withdraw from participation in the study at any time upon request.
Since the outcomes are all fairly immediate to the transplant procedure itself, it is unlikely that there would be scope for withdrawal from the study after the procedure has taken place.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 SAFETY ASSESSMENTS

All data collection as outlined in the Schedule of Activities (Section 1.2) will be evaluated to assess the safety of utilizing DCD donor hearts as compared to DBD donor hearts for transplantation:

- Donor Characteristics
- Transplant Details
- PGD Scores
- Inotrope Support
- Right Heart Catheter Data
- Mechanical Circulatory Support Data
- Invasive Ventilator Support Data
- Patient Survival
- Graft Survival
- Post-Transplant Hemodynamics
- Immunosuppressive Medications & Induction (if applicable)
- ICU & Hospital Stay
- Heart Graft-Related AEs and SAEs

Procedures that will be completed during the study as part of regular standard of clinical care:

- Demographics/Characteristics
- Medical & Cardiac History
- Patient Visits
- Endomyocardial Biopsy (recipient)

8.2 METHOD FOR NRP - NORMOTHERMIC REGIONAL PERFUSION (NRP) PROCEDURES

1. NRP Donor Heart Selection

NRP Donor heart selection will occur as deemed clinically acceptable for transplantation per eligibility criteria outlined in Section 5.1

2. DCD Donor Withdrawal of Life Sustaining Treatment

- The location of WLST should be agreed in advance, and a spacious OR is reserved for the donor procedure
- The donor hematocrit should be > 30% and transfusion to this level may be required
- Heparin 30000 IU is administered at the time of WLST
- The local team are clear that mechanical asystole (not electrical asystole) represents circulatory arrest
- The pulmonary team agrees for the main PA to be transected immediately and therefore to perform the antegrade flush through a Y-type cannula
- Once WLST has occurred, communication regarding the donor's vitals between OPO and the organ procurement teams is essential.
- Functional warm ischemic time begins when the systolic blood pressure is less than or equal to 50mmHg. If the patient does not suffer circulatory arrest within 25 minutes of this time, then the heart will be declined. If the blood pressure rises above 50mmHg, then this clock is reset.
- The team will wait for 90 minutes from WLST. If circulatory arrest has not occurred in this time then the heart will be declined.

3. Surgical Protocol

The team comprises at a minimum two surgeons, two procurement technicians and one perfusionist.

Pre-Withdrawal of Support

- The ECMO circuit should be prepared including the Medtronic Affinity CP Blood Pump device and the CAPIOX FX25 Advance Oxygenator with Integrated Arterial Filter and Hardshell Reservoir.
  Prime solution:
    - 4 units packed red cells (approx. 1200mL)
    - 1.5 litre Plasmalyte
    - 50,000 units heparin
    - 1mmol/kg sodium bicarbonate (1mL/kg 8.4% solution)

- If a heat-exchanger is available, set the perfusate temperature to 37ºC
- Set up Mayo stand (surgeon side, on patient right)
    - Scalpel
    - Sternal saw (test to ensure working)
    - 2nd Sternal Saw Battery (test to ensure working)
    - Retractor
    - Metzenbaum scissors x2
    - Forceps x2
    - Tube clamps x2
    - Arterial cannula and 2-stage venous cannula
    - Bulb syringe with saline
- Set up second Mayo stand (assistant side, on patient left)
    - Metzenbaum scissors
    - Forceps x2
    - Angled vascular clamps x3
    - Cardioplegia needle
- Ensure suction available/ adequate (ideally 3, two for chest, one for abdomen)
- Discuss roles/plan with all teams and OR staff

When the donor suffers circulatory arrest, or death is clearly imminent, the surgeons should do their final scrub.

Retrieval Procedure

- Patient is positioned, prepped, and draped
- Incision made, sternum divided with saw
- Pericardium widely opened with scissors
- The surgeon pulls down on the aortic arch while the assistant clamps in turn the innominate artery, left carotid artery and left subclavian artery.
- Arterial cannula inserted into the distal ascending aorta through a stab incision (the surgeon performs and the assistant holds this in place with their right hand). The surgeon clamps the cannula and connects to the red line of the ECMO circuit. Third scrubbed person fills the cannula/tubing with saline as the connection is made.
- Venous cannula inserted to right atrium through a stab incision (the surgeon performs and the assistant hold this in place with their left hand). The surgeon clamps the cannula and connects to the blue line of the ECMO circuit. Third scrubbed person fills the cannula/tubing with saline as the connection is made.
- The perfusionist starts the ECMO flow and records the time.
- Flow rates of 2 L/min should be targeted initially, until the RA cannula is fixed in place to avoid entrainment of air. The air/O2 mixer should be set to deliver a gas flow of 2L/min with a starting FIO2 of 21%. Once the circuit is stable, the flow can be increased to 3-5L/min, aiming for an SVO2 60-90%, pH 7.35-7.45, Hematocrit > 20% and pCO2 35-45mmHg, with a mean BP of 60-70mmHg. An

infusion of vasopressin may be required to support the BP. Field suction may augment the blood return to the venous reservoir.

- At this point all the organs are perfused, and the donor situation is analogous to the DBD donor. The abdominal team can continue with their dissection and assessment. The thoracic teams should secure their cannulae and continue with their dissection and assessment including the lungs. The donor can be re-intubated at this point and bronchoscopy performed.
- After a minimum of 20 minutes on ECMO, ventilation of the lungs can be fully resumed and the ECMO can be weaned with the heart taking over the circulation.
- Heart function is assessed from systemic blood pressure, CVP and visual examination, and if deemed adequate, the recipient procedure can be triggered.
- If the heart function is inadequate (or indeed the lung function is inadequate) it may be necessary to resume ECMO to support the abdominal organs.
- Once all teams are ready, timing of cross-clamp, delivery of preservation solutions and explantation of the heart (and other organs) proceeds exactly as for DBD donors.
- The heart is placed in cold storage for transport.

Stepwise procedure

Primary Surgeon	**Assistant Surgeon**
Skin incision Sternotomy Place sternal retractor Open pericardium	Pass off suction Secure the ECMO tubing
Pull down on the aortic arch and free the origins of the supra-aortic vessels	Clamp each supra-aortic vessel
Aortic cannulation, clamp and connect to red line	Secure aortic cannula
RA cannulation, clamp and connect to blue line	Secure RA cannula
Instructs perfusionist to commence ECMO	
Places purse-strings to secure the aortic and RA cannulae	
Manages the circulatory indices	Places field suction

8.3 METHOD FOR DPP - DIRECT PROCUREMENT AND PERFUSION (DPP) PROCEDURES

1. DPP Donor Heart Selection

In the event that Normothermic Regional Perfusion (NRP) for organ procurement is contraindicated or prohibited by the donor hospital, Direct Procurement and Perfusion (DPP) methods will be utilized. DPP Donor heart selection will occur as deemed clinically acceptable for transplantation per eligibility criteria outlined in Section 5.2.

2. DCD Donor Withdrawal of Life Sustaining Treatment

- The location of WLST should be agreed in advance, and a spacious OR is reserved for the donor procedure
- The donor hematocrit should be > 30% and transfusion to this level may be required
- Heparin 30,000 IU is administered at the time of WLST
- The local team are clear that mechanical asystole (not electrical asystole) represents circulatory arrest
- The liver team agrees to hold off perfusion until the cardiac team have drained enough donor blood for OCS priming (typically no more than 60 seconds)
- The pulmonary team agrees for the main PA to be transected immediately and therefore to perform the antegrade flush through a Y-ed cannula
- Once WLST has occurred, communication regarding the donor's vitals between OPO and the organ procurement teams is essential.
- Functional warm ischemic time begins when the systolic blood pressure is less than or equal to 50mmHg. If the patient does not suffer circulatory arrest within 25 minutes of this time, then the heart will be declined. If the blood pressure rises above 50mmHg, then this clock is reset.
- The team will wait for 90 minutes from WLST. If circulatory arrest has not occurred in this time, then the heart will be declined.
-

3. Surgical Protocol

The team comprises at a minimum two surgeons and two procurement technicians, one of whom is the trained OCS operator, and one perfusionist.

Pre-Withdrawal of Support

- OCS system preparation:
    - The OCS disposable module should only be opened when the donor has met cardiac arrest, but several elements should be prepared in advance
        - The OCS operator should take charge of the blood collection bag (30,000 IU of heparin inside) as well as reservoir additions, maintenance solution, levothyroxine solution and epinephrine solution
        - The 2nd transplant practitioner should take charge of the Del Nido cardioplegia, connect defibrillator to OCS module and communication
        - The back table prep for OCS instrumentation should also be set up sterile in advance (aortic connectors, 4x pledgeted sutures and free pledgets, needle driver, scissors, cable ties and gun, purse string suture for PA, tie for PA, PA cannula, suture for LV vent, LV vent, suture to close RA vent, suture to close IVC, pacing wire)
- Set up Mayo stand (surgeon side, on patient right)
    - Scalpel
    - Sternal saw (test to ensure working)
    - 2nd Sternal Saw Battery (test to ensure working)
    - Retractor

  - Metzenbaum scissors x2
  - Forceps x2
  - 2-stage venous cannula connected to primed collection bag (for blood collection)
- Set up second Mayo stand (assistant side, on patient left)
  - Metzenbaum scissors
  - Forceps x2
  - Cardioplegia needle
- Ensure suction available/ adequate (ideally 3, two for chest, one for abdomen)
- Discuss roles/plan with all teams and OR staff

When the donor suffers circulatory arrest, or death is clearly imminent, the OCS operator can install the OCS disposable module; and the surgeons should do their final scrub

Retrieval Procedure

- Patient is positioned, prepped, and draped
- Incision made, sternum divided with saw
- Pericardium widely opened with scissors
- Drainage cannula inserted to right atrium, collection bag dropped to patient right, and clamp removed
  - 1.2-1.5L of blood must be collected. It is essential that no preservation solution is given prior to blood collection.
  - Collection may be aided by placing the patient in Trendelenburg position
  - Communication with the abdominal team is key. Blood collection should take no more than 60 seconds
- While surgeon collects priming blood, the assistant places the cardioplegia needle and connects to the cardioplegia line
- After blood collected, the heart is vented via the IVC and pulmonary veins, the aorta is clamped, and 500ml del Nido cardioplegia is delivered
- Heart is excised in the standard fashion
- OCS setup as per standard

OCS Medication Kit

MEDICATION	QTY IN KIT
Levothyroxine 100mcg vial	2
Sodium chloride 0.9%, 100mL bag	1
Sodium bicarbonate 8.4%, 1mEq/mL (50mL vial)	1
(Solu-Medrol) Methylprednisolone 125mg vial	2
Epinephrine 1mg/1mL ampule	1
Ciprofloxacin 200mg/100mL bag	1
Cefazolin 1g vial	1

Heparin 3000 units/mL (10mL vial)	1
Dextrose 5% (500mL bag)	1
Calcium gluconate 10%, 100mg/1mL (10mL vial)	1
Sterile water for injection (10mL vial)	3
Albumin (Human) 25% (50mL vial) or (single 100mL vial if possible)	2
Lidocaine 1%, 10mg/mL (30mL vial)	1
Millex GV 0.22 Micron Filter Unit	2
5 micron 19G filter needle	2
Mannitol 25%, 12.5g/50mL (50mL vial)	1
Potassium Chloride 2mEq/mL (10mL vial)	1
Infuvite Adult multivitamin 2x5mL vials	1
Humulin R (regular insulin) 100 units/mL (3mL vial)	1
Del Nido Solution (1030 mL bag) Glyceryl Trinitrate (50 mg) Erythropoietin (2500 IU)	1 1 1

Stepwise procedure

Primary Surgeon	**Assistant Surgeon**
Skin incision Sternotomy Place sternal retractor Open pericardium	Pass off cardioplegia line Pass off suction
Open right atrial appendage and cannulate	Grasp right atrial appendage and assist
Secure cannula for blood collection, communication with abdominal team and procurement teams	Assist with collection of blood Verify cardioplegia line is flushed
Vent heart – IVC and pulmonary vein (or LAA if lungs also being procured)	Assist with venting, suction placement
Clamp aorta Place cardioplegia needle to ascending aorta (high as possible) Hold needle as cardioplegia given	Connect cardioplegia line and verify flow Apply ice to heart
Excision of heart	Assist with heart excision
Place heart on OCS	Assist with OCS

The decision to use the heart will depend on the appearance, flow/pressure parameters and lactate profile observed during perfusion. The recipient operation should be triggered following consideration of these factors and the travel time.

8.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Only Serious Adverse Events (SAEs) and Heart Graft-Related Adverse Events (HGRAEs) will be captured in this study.

8.4.1 HEART GRAFT-RELATED ADVERSE EVENTS (HGRAE)

All heart graft-related adverse events (HGRAEs) are to be recorded on the electronic case report forms until post-transplant day 30 or through hospital discharge if longer than 30 days. The description of the adverse event will include: the date of onset, duration, severity, seriousness, the relationship of the event to the trial treatment, anticipated or not, and any treatment required. The principal investigator is responsible for the classification and reporting of heart graft-related adverse events to the appropriate regulatory authorities.

8.4.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Serious adverse events will be collected only through Day 30 post-transplant. An adverse event will be classified as serious if it meets any of the following criteria:

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

8.4.3 DEFINITION OF HEART GRAFT-RELATED SERIOUS ADVERSE EVENTS (HGRSAE)

Heart Graft-Related SAEs are defined as:

- Moderate or Severe heart PGD (left or right ventricle) (not including rejection or cardiac tamponade) according to ISHLT consensus manuscript
- Primary graft failure requiring re-transplantation
- Use of post-transplant mechanical circulatory support (ECMO, LVAD, RVAD, BiVAD) for > 72 hours immediately post-transplant

- Lack of patient and/or graft survival at 30 days post-transplant
- Lack of patient and/or graft survival at initial hospital discharge, if later than 30 days post-transplant

HGRSAEs will be collected from the time a subject is transplanted until the completion of the 30-day follow-up evaluation. A HGRSAE will be followed until resolution or stabilization of the event.

8.4.4 CLASSIFICATION OF AN ADVERSE EVENT

8.4.4.1 SEVERITY OF EVENT

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

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

8.4.4.2 RELATIONSHIP TO STUDY INTERVENTION

The investigator will assess the relationship of the AE to the utilization of a DCD donor heart. The relationship will be assessed using the following categories:

- **Definitely Related** – There is a reasonable causal and temporal relationship between utilization of a DCD donor heart and the adverse event
- **Probably Related** – It is more likely than not that there is a reasonable causal relationship between utilization of a DCD donor heart and the adverse event
- **Possibly Related** – The There is a reasonable relationship with the utilization of a DCD donor heart and the adverse event, but the causal relationship is unclear or lacking
- **Unlikely Related** – There is a temporal relationship with the utilization of a DCD donor heart and the adverse event, but there is not a reasonable causal relationship between the trial device and the event
- **Unrelated** – There is no relationship between the utilization of a DCD donor heart and the adverse event

8.4.4.3 EXPECTEDNESS

The investigator will be responsible for determining whether an adverse event (AE) or serious adverse event (SAE) is expected or unexpected.

Anticipated SAEs that are associated with heart transplant procedures within the first 30 days after heart transplant includes, but is not limited to:

- Acute rejection
- Atrial and ventricular arrhythmias

- Bleeding (major)
- Hemodynamic instability
- Death
- Fever
- Infection
- Primary Graft Dysfunction
- Respiratory failure
- Graft failure
- Sepsis
- Renal dysfunction
- Hyperammonaemia
- Malignancy (post-transplant lymphoproliferative disorder (PTLD)
- Multiple organ failure
- Myocardial infarction
- Neurological dysfunction
- Hepatic dysfunction
- Diabetes due to steroid and anti-rejection medications
- Gall stones
- GI bleeding
- Pancreatitis
- Peptic ulceration
- Gastritis
- Gastro esophageal reflux disease (GERD)
- Pneumo-mediastinum
- Pneumothorax
- Hemothorax
- Pleural bleeding
- Pleural effusion
- Venous thromboembolism (deep venous thrombosis [DVT])
- Pulmonary embolism (PE)
- Sternal wound dehiscence
- Organ deemed not transplantable after retrieval
- Stroke
- Psychosis
- Cerebrovascular accident
- Peripheral vascular clotting or occlusion due insertion of mechanical support
- Limb gangrene due to vascular occlusion due insertion of mechanical support
- Use of mechanical circulatory support
- Coagulopathy
- Hyperacute rejection
- Anastomotic site complications; narrowing, bleeding or occlusion
- Delayed sternal wound closure due to compromised cardiac function or excessive bleeding or both
- Bowel thromboembolic complications and gangrene

8.4.5 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Subjects will be monitored before, during and after the operative procedure to help ensure their safety. The investigators are members of transplant teams who have extensive experience with heart transplantation. Subjects in the trial will undergo frequent visits and routine monitoring to help detect any abnormal changes and to provide appropriate treatment as necessary.

All heart graft-related events and any heart graft-related serious adverse events will be followed and documented until the investigator designates the event to be either resolved or its effect on the patient's condition is stabilized.

All heart graft-related adverse events and serious adverse events are to be recorded on the electronic case report forms until post-transplant day 30. The description of the adverse event will include: the date of onset, duration, severity, seriousness, the relationship of the event to the trial treatment, anticipated or not, and any treatment required. All serious adverse events occurring during the course of the first 30 days post-transplant will be documented on the appropriate electronic case report form(s) in REDCap. Heart graft-related AEs will be recorded up to the 30-day follow-up or through hospital discharge if longer than 30 days. The principal investigator is responsible for the classification and reporting of heart graft-related adverse events to the appropriate regulatory authorities.

8.4.6 ADVERSE EVENT REPORTING

All AEs captured throughout the duration of the study will be reported to the DSMB on a quarterly basis.

8.4.7 SERIOUS ADVERSE EVENT REPORTING

All SAEs captured throughout the duration of the study will be reported to the DSMB on a quarterly basis. It is the responsibility of the Principal Investigator to report all serious adverse events (SAEs) of concern (as defined in Section 7.1) to the DSMB within 24 hours of discovering the event.

8.4.8 EVENTS OF SPECIAL INTEREST

Not Applicable.

8.5 UNANTICIPATED PROBLEMS

8.5.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.5.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data and Safety Monitoring Board (DSMB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DSMB as soon as possible, but no later than 10 business days from the investigator's or study team's awareness of the event, incident, information or outcome.
- Any other UP will be reported to the IRB and to the DSMB within 10 business days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) as required.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Endpoint

- Comparison of the incidence of Heart Graft-related Serious Adverse Events (HGRSAEs) in the first 30 days post-heart transplantation for DCD heart transplanted recipients and DBD heart transplanted recipients.

Secondary Endpoints

- Comparison of length of time on waiting list for DCD hearts to:
  - Time on waiting list for DBD heart for that patient
  - Median time for a DBD heart transplant recipient matched for height and ABO group
- Utilization rates of heart offers, donors attended, and hearts explanted in DCD donors as compared to DBD donors
- Cost per DCD transplant and cost saving per DCD transplant (especially for in-patients/MCS patients)

9.2 SAMPLE SIZE DETERMINATION

The study is intended to serve as a proof-of-concept study. Comparative analyses will be primarily descriptive due to a small sample size.

9.3 POPULATIONS FOR ANALYSES

All heart transplanted recipients during the study period (both DCD recipients and DBD recipients) will be included in analyses.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

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

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

Safety Analysis

Serious Adverse Events (SAEs) and Heart Graft-related Serious Adverse Events (HGRSAEs) will be collected within the first 30 days post-transplant and the mean number of HGRSAEs per subject will be summarized using descriptive statistics. HGRSAEs are defined as the following adverse events (at most one per type):

- Moderate or Severe heart PGD (left or right ventricle) (not including rejection or cardiac tamponade)
- Primary graft failure requiring re-transplantation
- Patient and graft survival at 30 days post-transplant
- Patient and graft survival at 30 days and initial hospital discharge, if later than 30 days
- Use of post-transplant mechanical circulatory support (ECMO, LVAD, RVAD, BiVAD) for > 72 hours immediately post-transplant.

SAEs and HGRSAEs will also be tabulated using counts and percentages alone and in regards to the relationship of the HGRSAE to the study intervention, and the severity of the HGRSAE.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary endpoints will be analyzed in a manner analogous to the primary endpoint, inclusive of transplant recipients who receive a DCD or DBD heart during the study period.

9.4.4 BASELINE DESCRIPTIVE STATISTICS

Baseline descriptive statistics will apply to demographic and clinical descriptions of the study cohort.

9.4.5 PLANNED INTERIM ANALYSES

Not Applicable. See section 10.1.6 for description of DSMB safety oversight and study stopping rules.

9.4.6 SUB-GROUP ANALYSES

Not Applicable.

9.4.7 EXPLORATORY ANALYSES

Not Applicable.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

All patients on the heart transplant waiting list at Cedars-Sinai will be identified by trial investigators and screened for trial eligibility. Those patients who initially appear eligible for the trial will have the trial

thoroughly explained to them by a trial investigator, be invited to participate, and will be asked to sign an informed consent. Consent of a legally authorized representative of a cognitively impaired individual will be obtained before the cognitively impaired individual may be included in research.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- DSMB extermination of unexpected, significant, or unacceptable risk to participants or meeting one of the stopping rules.
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the DSMB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators and their staff. This confidentiality is extended to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Cedars Sinai Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be

identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Cedars Sinai Medical Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at Cedars Sinai Medical Center.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Not applicable.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator
Fardad Esmailian, MD
Surgical Director, Heart Transplantation and Mechanical Circulatory Support
Clinical Chief, Department of Cardiac Surgery
Cedars-Sinai Heart Institute
127 S. San Vicente Blvd., Suite A3103, Los Angeles CA 90048

10.1.6 SAFETY OVERSIGHT

An independent Data and Safety Monitoring Board (DSMB), comprised of expert physicians in the related field who are not participating in the trial, will perform monitoring activities to ensure the identification, documentation, and analysis of adverse events; and to ensure compliance with the protocol and procedures that are in place for conducting research to protect the safety and well-being of all subjects. The DSMB will have a formal meeting at least once annually. Frequency of the meetings may be changed by the DSMB in consultation with the Principal Investigator based on need. An ad hoc meeting may be called at any time by the DSMB Chairperson or by the PI and research staff should ethical or patient safety issues arise.

A status update will also be provided to the DSMB on a quarterly basis via email correspondence by the DSMB Coordinator.

Section 7.1 outlines criteria for suspension of enrollment/DCD donor heart utilization until review by the DSMB. It is the responsibility of the Principal Investigator to report all of the above SAEs to the DSMB within 24 hours of discovering the event.

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

An internal auditor will regularly review the conduct of the trial, verify adherence to the protocol, and confirm the completeness, consistency, and accuracy of all documented data.

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All data collected will already exist in the medical record under standard of care.

Data will be reviewed from between the dates of 3/01/2022 to 9/01/2023. Data will be collected from the following timepoints: post-heart transplant Day 0, Day 7, Day 14, Day 30 and at hospital discharge. Data will be collected prospectively and retrospectively.

The following data points/variables will be collected:

- Incidence of primary graft dysfunction
- Initial use of mechanical circulator support: The use of ECMO, intra-aortic balloon, LVAD, RVAD or biVAD
- Number of inotropes/pressors at 24 hours post-transplant
- Inotropic support for first 72 hours: The following inotropic medication doses will be collected at ICU admission T0, T12, T24, T48, and T72 hours after ICU admission post-heart transplantation:
    - Dopamine – mcg/kg/min
    - Dobutamine – mcg/kg/min
    - Amrinone – mcg/kg/min
    - Milrinone – mcg/kg/min
    - Epinephrine – mcg/kg/min
    - Norepinephrine – mcg/kg/min
- Initial use of mechanical respiratory support: Duration of initial post-transplant invasive ventilator support from time of initial admission to ICU post heart transplant until extubation
- Immunosuppression Medications (at day 7 and at time of discharge)
- Incidence of reperfusion injury on endomyocardial biopsy
- Cardiac index
- Cardiac output
- Blood pressure
- Mean arterial pressure
- Pulmonary artery pressure
- Pulmonary capillary wedge pressure
- Left atrial pressure
- Right atrial pressure
- Right ventricular pressure
- Stroke volume
- Ejection fraction

- BUN and Creatinine
- Liver function tests
- Cellular rejection
- Antibody mediated rejection
- Graft related serious adverse events
- Mitochondrial function
- Age at transplant
- Sex
- Donor characteristics
- Total cross clamp duration in minutes
- Ischemic time
- Surgical complications
- Total length of stay
- ICU length of stay
- Total blood products used
- Trans-thoracic echocardiogram results prior to discharge:
    - Ejection Fraction (EF%)
    - Wall motion assessment
    - LV Septal and posterior wall thickness
    - Any valve abnormalities
- Patient and graft survival at day 30
- Incidence of acute cellular rejection in the first 30 days post heart transplant
- Incidence of antibody mediated rejection in the first 30 days post heart transplant
- Adverse events: All heart graft-related serious adverse events and any heart graft-related adverse events will be followed and documented until the investigator designates the event to be either resolved or its effect on the patient's condition stabilized.
- Medications: Medications used to treat all serious heart graft-related adverse event (SAE)-related until the SAE is resolved.
- Financial data related to transplant procedure
- Donor heart utilization rates

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

During each subject assessment, an investigator participating in the trial will record progress notes to document all significant observations. In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes.

All data required by the trial protocol will be completely and accurately entered into the REDCap database by the investigator or his or her designate, identifying subjects by subject number. Essential trial documents must be maintained by the Investigator for at least 7 years.

Storage of Physical Records: Physical records will be maintained for this study at a secure location where access is limited to approved personnel. The records will not be removed from Cedars-Sinai premises.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap a 21 CFR Part 11-compliant data capture system provided by Cedars Sinai Medical Center. Clinical data will be entered directly from the source documents.

Secure storage: Data will be housed in a HIPAA-compliant secure storage system, like REDCap or Box, within the Cedars-Sinai network with access restricted to approved members of the research team.

Limited Access: Private identifiable information, will be accessible only to IRB approved study team members with current IRB training.

Unique ID Numbers: Each patient will be assigned a unique ID number, which will be used to code data and specimens

10.1.8.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 2 years after the conclusion of the study.

10.1.9 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or institutional regulatory requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. Any protocol deviations made in order to eliminate apparent immediate hazard to a research subject must be reported to the IRB within 5 business days. All deviations must be addressed in study source documents. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements and reporting timelines of deviations.

10.1.10 PUBLICATION AND DATA SHARING POLICY

This study will comply with Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 2 years after the completion of the primary endpoint by contacting the Principal Investigator.

10.1.11 CONFLICT OF INTEREST POLICY

Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

10.2 ABBREVIATIONS

AE	Adverse Event
BP	Blood Pressure
CFR	Code of Federal Regulations
CPB	Cardiopulmonary bypass
CRF	Case Report Form
CVP	Central Venous Pressure
DBD	Donation after Brain Death
DCD	Donation after Circulatory Death
DSMB	Data Safety Monitoring Board
DPP	Direct Procurement and Perfusion
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FIO2	Fraction of Inspired Oxygen
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
HGRAE	Heart Graft-Related Adverse Event
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISHLT	International Society for Heart and Lung Transplantation
IU	International Unit
IVC	Inferior Vena Cava
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
NCT	National Clinical Trial
NRP	Normothermic Regional Perfusion
OCS	Organ Care System
OHRP	Office for Human Research Protections
OPO	Organ Procurement Organization
PA	Pulmonary Artery
pCO2	Partial Pressure of Carbon Dioxide
PGD	Primary Graft Dysfunction
PI	Principal Investigator
RA	Right Atrium
SAE	Serious Adverse Event
SOA	Schedule of Activities
SVO2	Mixed Venous Oxygen Saturation
TTE	Transthoracic Echocardiogram
UP	Unanticipated Problem
US	United States
WLST	Withdrawal of Life Sustaining Treatment

10.3 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
V 1.0	12May2022	-	-

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