Randomized Trial to Compare the SherpaPak™ Device vs Cold Storage of Donor Hearts in Transplantation: A Pilot Study

Version 3, February 16, 2022

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PROTOCOL SUMMARY

Purpose and Knowledge to be Gained	The purpose the research is to compare the SherpaPak™ Cardiac Transport System to standard of care cold storage of donor hearts for transplantation. Successful use of this device may decrease cold injury of donor hearts by maintaining the temperature consistently during transport and therefore may decrease primary graft dysfunction after transplantation.
Research Procedures	The primary research procedure is the use of the SherpaPak Cardiac Transport System for the preservation and transport of donor hearts for transplantation
Subject Population	Patients listed for heart transplant at Cedars-Sinai
Duration	The study includes 6 visits. The total study duration is 30 days

GENERAL INFORMATION

Sponsor/Funder	Internally Funded
Collaborating Institutions Involved in the Research	Not Applicable

PROTOCOL AMENDMENT HISTORY

Protocol Version	**Summary of Changes/Rationale for Changes**
Protocol V3: February 16, 2022	- Removed CSMC Co-Investigators section under General Information as this section would be too large - Section 3.3 Exclusion Criteria removed all exclusion criteria - Section 4.0 Study Design, Schedule of Procedures updated to add Randomization at Visit 1, extend the visit #6 window and clarify timing of biopsy tissue collection - Section 5.1 Data Procurement removal of AHD Registry language as this registry will not be utilized - Minor revisions throughout protocol for clarity - Section 6.0 Data Safety Monitoring, language regarding the DSMB Charter has been inserted - Formatting revised throughout
Initial Protocol V2: July 15, 2021	N/A

1.0 BACKGROUND, RATIONALE

Cardiac transplantation is currently the procedure of choice for selected patients with end-stage heart disease that is not amenable to further medical intervention or conventional cardiac procedures. Successful organ preservation is an important component of transplantation and ensures the maintenance of organ viability until implantation into the recipient. Currently, heart preservation for transplantation is limited to 4 to 6 hours of cold ischemic storage. Longer periods of ischemia are associated with poor outcomes post transplantation. In heart transplantation, preservation injury and ischemic reperfusion injury contribute to microvascular dysfunction and myocardial injury leading to primary graft dysfunction or to the activation of pro-inflammatory and pro-fibrotic processes, and the development of cardiac fibrosis and allograft vasculopathy.

In general, instructions for the use of organ preservation solutions state a temperature range of 2-8°C or 4-8°C, balancing the risk of cold injury at lower temperatures against the risk of hypoxic injury at higher temperatures. The standard method of storing donor hearts in preservation fluid within sequential bags that are then placed on ice and transported in a cooler does not allow for exact temperature control. The SherpaPak™ Cardiac Transport System has been developed to provide a safe, consistent method for cold ischemic storage of donor hearts for transplantation. Successful use of this device may decrease cold injury of donor hearts by maintaining the temperature consistently during transport and therefore may decrease primary graft dysfunction after transplantation.

2.0 STUDY OBJECTIVES

Primary Objective
To compare the SherpaPak™ Cardiac Transport System to standard of care cold storage of donor hearts for transplantation.

Secondary Objective
To assess for a decrease in cold injury of donor hearts and therefore a decrease in primary graft dysfunction. To assess for events between study groups.

Primary Endpoint
The primary endpoint will be a composite endpoint of: Absence of moderate to severe primary graft dysfunction per ISHLT grading scale (left or right ventricle) in the first 24 hours post transplantation, and 30-day patient survival, 30-day incidence of ischemic reperfusion injury on endomyocardial biopsies and changes in mitochondria function and quality (at donor heart harvesting, at the time just prior to donor heart implantation and at one-week post- heart transplantation).

Secondary Endpoints – To describe between the groups

1. Each individual component of the composite endpoint will be assessed.
2. Hemodynamic parameters including cardiac index, cardiac output, blood pressure, mean arterial pressure, pulmonary artery pressure, left atrial pressure, right atrial pressure, right

ventricular pressure, stroke volume and ejection fraction at 24 hours post-transplant
3. The number of inotropes/pressors at 24 hours post -transplant.
4. Incidence of acute cellular rejection in the first 30 days post heart transplantation.
5. Incidence of antibody mediated rejection in the first 30 days post heart transplantation.
6. Incidence of heart graft related Serious Adverse Events in the first 30 days post heart transplantation.
7. Total length of stay
8. ICU length of stay
9. Number of blood products used

3.0 STUDY POPULATION

3.1 SELECTION OF THE STUDY POPULATION

- Study subjects will be drawn from patients listed for heart transplant at Cedars-Sinai Medical Center.

3.2 INCLUSION CRITERIA

- Any sex/gender, 18 years of age or older listed for heart transplant.
- 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.
- Signed: 1) written informed consent document and 2) authorization to use and disclose protected health information
- Subjects must receive and accept a non-local donor offer (from Northern California, Arizona, Nevada or farther geographies)

3.3 EXCLUSION CRITERIA

Not Applicable

3.4 SUBJECT SCREENING AND ENROLLMENT

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.

When a matching donor heart becomes available, the 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 they will exit the study and no information will be collected for these patients.

If the subject is matched with a donor heart from a local donor (Southern California), the

subject will be considered a screen failure and they will exit the study and no information will be collected for these patients.

When a matching donor heart from a non-local donor offer (from Northern California, Arizona, Nevada or farther geographies) becomes available the recipient will be assigned a subject identification number and randomized 1:1 to receive a heart transported using either standard of care cold storage or the SherpaPak™ Cardiac Transport System. REDCap will be used for randomization.

3.5 SUBJECT RECRUITMENT

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.

4.0 STUDY DESIGN AND METHODS

This study is designed to be conducted as a single-center randomized prospective trial to compare the SherpaPak™ Cardiac Transport System to standard of care cold storage for donor hearts in transplantation. Approximately 20 consented subjects will receive a donor heart transported using either cold storage or the SherpaPak™ Cardiac Transport System, respectively. Both methods are FDA approved.

Donor hearts will be screened for eligibility based on current standard of care criteria. Heart transplant candidates will be screened for trial eligibility. Every eligible candidate will be asked to participate. Eligible and consented transplant candidates will receive donor hearts transported using standard of care cold storage or the SherpaPak™ Cardiac Transport System, that have been deemed clinically acceptable for transplantation by the treating transplant clinical team.

The study will be evaluating the comparative use of two FDA-approved methods for organ procurement. The research procedures will be randomization, data collection/analysis, and tissue collection from standard of care biopsies for mitochondrial testing.

Mitochondrial Testing

Biopsy tissue from donor hearts will be collected prior to transport, prior to transplant and at one-week post-transplant. The tissue will be evaluated to detect changes in mitochondrial function and regulation.

Biopsy tissue will be processed and stored by the Gottlieb Laboratory at Cedars-Sinai. The Gottlieb Laboratory, led by Roberta A. Gottlieb, MD, is studying the molecular mechanisms regulating mitochondria in the heart's response to ischemic injury.

4.1 SCHEDULE OF PROCEDURES

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 ± 14 days)
Eligibility & Informed Consent	X						
Demographics/Characteristics	X						
Medical & Cardiac History	X						
Confirm Eligibility/Randomize		X					
Data Collection Donor Characteristics		X					
Patient Visit (recipient)	X	X	X	X	X	X	X
Tissue Collection for biopsy (donor heart prior to transport & prior to transplant)		X	X				
Mitochondrial Testing		X	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
Data Collection Immunosuppressive Meds & Induction (if applicable)		X	X			X	X
Data Collection ICU & Hospital Stay						X	
Data Collection Heart Graft-Related AEs and SAEs		X	X	X	X	X	X

5.0 DATA COLLECTION AND MANAGEMENT

5.1 DATA PROCUREMENT

Except for mitochondrial studies (research), all data collected will already exist in the medical record under standard of care. Tissue collected will undergo mitochondrial studies.

5.2 TIME PERIOD OF DATA UNDER REVIEW

- Data will be reviewed from the dates of 9/01/2021 to 8/31/2023. 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.
- Information will be kept in REDCap for two years after the conclusion of the study.

5.3 VARIABLES COLLECTED

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 events (SAEs) until the SAE is resolved.

5.4 SOURCE DOCUMENTS

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

5.5 DATA COLLECTION AND STORAGE

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

5.6 CONFIDENTIALITY AND SECURITY OF DATA

- **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.

6.0 DATA AND SAFETY MONITORING

6.1 DATA AND SAFETY MONITORING PLAN

Safety will be analyzed principally by examination of the frequency of adverse events. In particular, the number of donor heart graft-related serious adverse events (SAEs) up to the 30-day follow-up after transplantation per subject will be analyzed. This endpoint is defined to consist of the following adverse events (at most one per type), if they are serious adverse events:

- Primary heart graft dysfunction (not including rejection or cardiac tamponade):
    - Use of ECMO, RVAD, LVAD, BiVAD or insertion of a new IABP for >12 hours post TX.
    - Use of ≥ 2 inotropic agents/vasopressors including high-dose epinephrine or norepinephrine for >7 days post heart TX.
    - Open chest post heart TX. due to compromised heart function
- Primary graft failure requiring re-transplantation

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 transplants and who will be trained to use the SherpaPak Cardiac Transport System to further minimize risk.

Subjects in the trial will undergo frequent visits and routine monitoring to help detect any abnormal changes and to provide appropriate treatment as necessary.

An independent Data and Safety Monitoring Board (DSMB) comprised of two expert heart failure physicians and one cardiothoracic surgeon 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 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.

The criteria below provide guidance for suspending trial enrollment/randomization until review by the DSMB. 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 use of a mechanical circulatory support (MCS) device within 24 hours after transplant in subjects randomized to the SherpaPak method of transport.
- Two (2) deaths occur in subjects randomized to the SherpaPak method of transport 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.

In the event that the study is suspended, no new subjects will be consented or randomized to the trial. Subjects already in follow-up on the study will continue to be followed as outlined in the protocol unless the appointed Chair provides further recommendations.

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.

A SAE is any AE that in the view of the Investigator results in death, is life-threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization. In the interest of patient safety, and in order to fulfill regulatory requirements, all SAEs (regardless of their relationship to the study procedures) will be documented and reported per IRB guidelines. In the interest of this study, the SAEs that meet the stopping rule criteria within the DSMB Charter, will be submitted to the DSMB for review.

Heart-graft related-AEs will be captured in this study. The investigator will assess the relationship of the AE to the SherpaPak Cardiac Transport System or to the standard of care methods of preservation. The relationship will be assessed using the following categories:

- Definitely Related: There is a reasonable causal and temporal relationship between preservation with the SherpaPak Cardiac Transport System and the adverse event.
- Probably Related: It is more likely than not that there is a reasonable causal relationship between preservation with the SherpaPak Cardiac Transport System and the adverse event.
- Possibly Related: There is a reasonable relationship with preservation with the SherpaPak Cardiac Transport System and the adverse event, but the causal relationship is unclear or lacking.
- Unlikely Related: There is a temporal relationship with preservation with the SherpaPak Cardiac Transport System and the adverse event, but there is not a reasonable causal relationship between the trial device and the event.
- Unrelated: There is no relationship between preservation with the SherpaPak Cardiac Transport System and the adverse event.

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

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

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

- All relevant correspondences and required reports that pertain to the trial
- Records of receipt, use or disposition of the investigational device, including the type and quantity of the device; the dates of receipt; the lot number; the names of all persons who received, used or disposed of each device; and why and how any units of the device have been returned to the Sponsor, repaired, or otherwise disposed
- Records of each subject's case history and exposure to the device
- Signed and dated consent forms
- Protocol, and any amendments
- Investigator curriculum vitae

6.2 QUALITY CONTROL AND QUALITY ASSURANCE

- The investigator is required to keep accurate records to ensure that the conduct of the study is fully documented. 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.

7.0 STATISTICAL CONSIDERATIONS

7.1 STUDY OUTCOME MEASURES

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.

7.2 SAMPLE SIZE CONSIDERATIONS

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

8.0 REFERENCES

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