Monitoring Organ Donors to Improve Transplantation Results (MOnIToR) trial methodology

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ABSTRACT

Background: Despite efforts to increase organ donation, there remain critical shortages in organ donors and organs procured per donor. Our trial is a large-scale, multicentre, randomised controlled trial in brain-dead donors, to compare protocolised care (using minimally invasive haemodynamic monitoring) with usual care. We describe the study design and discuss unique aspects of doing research in this population.

Methods: Our study will randomise brain-dead patients to protocolised or usual care. The primary end point is the number of organs transplanted per donor. Secondary end points include number of transplantable organs per donor, recipient 6-month hospital-free survival time, and the relationship between the level of interleukin-6 and the number and usability of organs transplanted. The primary analysis will be an intention-to-treat analysis; secondary analyses include modified intention-to-treat and as-treated analyses. The study will also compare the ratio of observed to expected number of organs transplanted per donor, by treatment arm, as a secondary end point. Preplanned subgroup analyses include restriction to extended criteria donors, and donors older or younger than 65 years.

Results and conclusions: Several unique challenges for study design and execution can be seen in our trial, and it should generate results that will inform and influence the fields of organ donation and transplantation.

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Background and rationale

Donation after neurological determination of death (DNDD) remains the most common form of organ donation. Despite efforts to increase organ donation, there is still a critical shortage of organ donors and organs procured per donor.[1] The average number of organs transplanted per DNDD donor is just over three.[1] Furthermore, many donors may be lost to cardiovascular collapse or conversion to donation after cardiovascular determination of death (DCDD). Such progression results in the loss of 10%–20% of potential donors.[2,3]

Compared with historical controls, donor management that included aggressive fluid resuscitation has been shown to reduce cardiovascular collapse and increase organ yield.[4] However, small changes in hydrostatic pressure may result in substantial increases in lung water, owing to changes in the permeability of the lung. For this reason, many experts recommend avoiding aggressive fluid resuscitation.[3,5,6] This is not only important for lung donors, but may avoid hypoxaemia or the need for injurious mechanical ventilation, which may further worsen systemic inflammation.[7] Management of the haemodynamic status of the donor aims to achieve euvolaemia, maintain blood pressure and optimise cardiac output. This is to achieve gradients of perfusion pressure and blood flow that promote organ function with minimal use of vasoactive drug support. Adequate fluid resuscitation while avoiding fluid overload requires precise minute-to-minute data on fluid status.

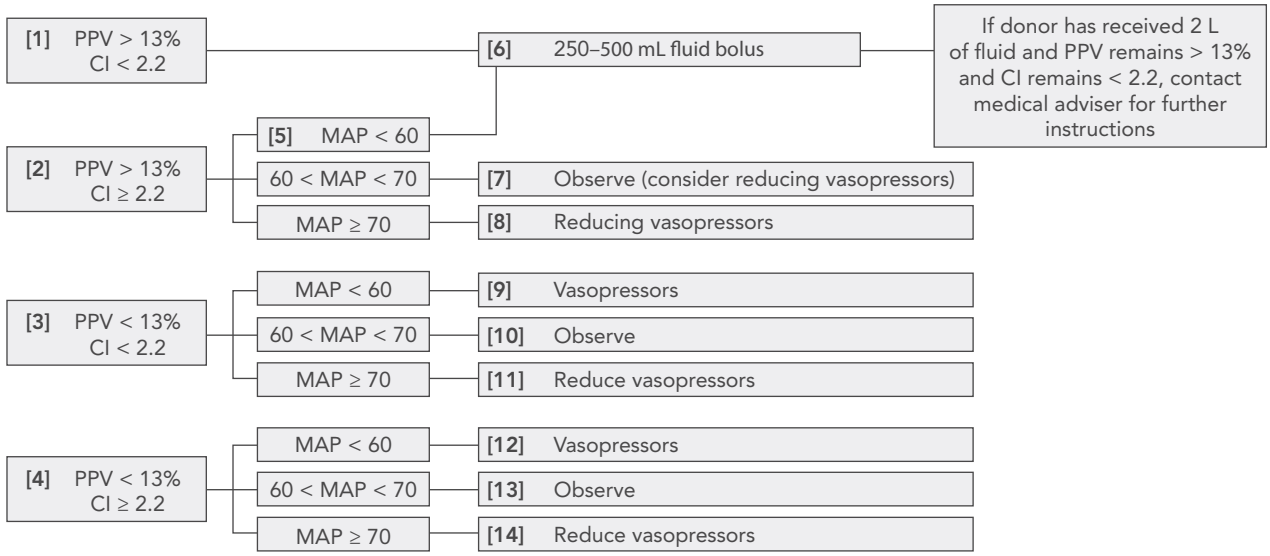
Organ donation abbreviations

CORID	Committee for the Oversight of Research Involving the Dead
DCDD	donation after cardiovascular determination of death
DNDD	donation after neurological determination of death
ECD	extended criteria donors
IRB	institutional review board
MOnIToR	Monitoring Organ Donors to Improve Transplantation Results
OPC	organ procurement coordinator
OPO	organ procurement organisation
SRTR	Scientific Registry of Transplant Recipients
UNOS	United Network for Organ Sharing

There are several reasons why not all potential organs are donated. One of the most important is haemodynamic instability of the donor. This can be caused by several factors (eg, autonomic dysfunction, hypovolaemia, cardiac dysfunction or release of inflammatory mediators) and optimal resuscitation with fluids and appropriate use of vasopressors and inotropes is the only practical management strategy currently available. In an observational study, Murugan et al found that nearly half of organ donors were volume responsive, and that this state was associated with increased inflammatory mediators, associated in turn with fewer

Figure 1. Monitoring Organ Donors to Improve Transplantation Results intervention algorithm

A 1-day workshop was held in Pittsburgh in the summer of 2007, followed by web conferences in the summer and autumn of 2007. The planning committee consisted of transplantation experts (see Appendix), who developed a consensus-based algorithm for donor resuscitation based on blood pressure (mean arterial pressure [MAP], in mmHg), cardiac index (CI) and pulse pressure variation (PPV).



organs transplanted per donor.[8] Volume-responsive donors have higher levels of circulating inflammatory mediators (cytokines and related molecules), particularly interleukin (IL)-6, and were associated with organ failure that often persisted following transplantation, possibly leading to reduced survival in recipients. In a separate study, plasma IL-6 levels in donors just before explantation were shown to predict 6-month hospital-free survival (6mHFS) time in recipients.[9]

In the Unites States, dead organ donors are managed by independent organ procurement organisations (OPOs). In preparation for this trial, we surveyed several OPOs about devices used for haemodynamic monitoring. While most donors were managed with an arterial line, other monitoring methods (eg, central venous and pulmonary arterial catheters) were uncommon. Accordingly, we decided to use a functional haemodynamic monitor with its arterial waveform-derived variables, specifically, pulse pressure variation (PPV).

Design

Overview

The Monitoring Organ Donors to Improve Transplantation Results (MOnIToR) trial is a multicentre, randomised controlled trial comparing protocolised intervention against usual care in eight OPOs. Participating OPOs are listed in the Appendix. It is notable that our study is being conducted with OPOs, not with individual hospitals. Furthermore, each OPO manages organ donation for multiple hospitals, and our trial is a pragmatic one in which the intervention is provided by OPO personnel, and data collection is limited to elements collected for federal reporting requirements and haemodynamic data captured by the monitoring device. Subjects are randomly allocated to protocolised resuscitation using a consensus-based PPV-guided algorithm (Figure 1) versus usual care, using a 1:1 randomisation scheme.

Population

All DNDDs referred to participating OPOs are eligible if they fulfil all inclusion criteria and no exclusion criteria.

Inclusion criteria

- Brain death already declared according to local hospital criteria.
- Suitability established by the local OPO (donor meets standard or extended criteria for donation).
- Functioning arterial catheter at any site is in place.

Exclusion criteria

- Informed consent cannot be obtained from donor's authorised representative.
- Donor is younger than 16 years.
- Minimally invasive haemodynamic monitoring with a lithium dilution cardiac output (LiDCO) device cannot be performed.

- Lithium therapy was received by donor before brain death.
- Donor has severe aortic regurgitation, intracardiac shunt or is on intra-aortic balloon pump.
- Donor is receiving extracorporeal membrane oxygenation or ventricular assist device support.
- Donor was previously enrolled in an experimental protocol in which cytokines were the therapeutic targets (eg, anti-tumour necrosis factor [anti-TNF] antibodies).
- Donor had received chemotherapy or has any condition (eg, AIDS) that results in leukopenia (ie, white blood cell [WBC] count $< 2 \times 10^9$/L).
- Donor had received antileukocyte drugs (eg, muromonab-CD3 [OKT3]), regardless of the WBC count.
- Pregnancy.

In order to be inclusive and generalisable, we decided to include both standard and extended criteria donors.

Enrolment

Enrolment began in 2009. Organ procurement coordinators (OPCs) obtain consent for participation in the study, usually with consent for donation from the next of kin or legal representatives. Consent procedures follow local requirements, as approved by OPO review committees, as well as the University of Pittsburgh Committee for the Oversight of Research Involving the Dead (CORID). Where required, additional approval by local institutional review boards (IRBs) is sought. Once consent is obtained, entry criteria and other baseline data are entered into a web-based enrolment application. Assuming entry criteria are met, the subject is enrolled using his or her United Network for Organ Sharing (UNOS) identification number, and treatment allocation is randomly assigned. Randomisation is 1:1 into each trial arm, by variable block, by each OPO.

Intervention

PPV during mechanical ventilation when there is no spontaneous breathing (as is the case in DNDD) is highly accurate, sensitive and specific in predicting volume responsiveness.[10-12] We considered and evaluated many devices that use PPV as a variable, and the consensus was to use a calibrated system (LiDCO*plus*, LiDCO Group) so as to obtain an accurate cardiac index in circumstances of potentially rapid changes in systemic vascular resistance.

After enrolment, OPCs are responsible for setting up and calibrating the LiDCO device for donors randomly allocated to the protocolised care arm (the procedure takes about 15–20 minutes and need only be performed once, even if there is an interruption in monitoring due to patient transport or other reasons). Continuous, beat-to-beat haemodynamic data, including cardiac output, mean arterial pressure and PPV parameters are stored on the device for 6 months, and can be downloaded using a universal serial bus (USB) device.

The protocol algorithm (Figure 1) is used in conjunction with a web-based data collection tool. This tool is used by the OPC for subjects in the usual-care arm (but without the algorithm) to ensure equivalent data collection. Study intervention and data collection continue until the patient is transferred to the operating room for organ procurement.

Education to ensure proper implementation of the study protocol has been done via web-based training. Project managers conduct monthly conference calls with the OPCs to ensure they are kept updated in all aspects of the protocol.

Control arm

Apart from the intervention, there are numerous aspects of donor care that vary across OPOs, and sometimes within OPOs across individual care providers. It is neither feasible nor desirable to standardise all these care aspects. For example, we do not specify the choice of intravenous fluids, vasopressors, antihypertensive agents or other aspects of care. Regulating these aspects of care would be very difficult and are not the focus of this study. The choice of intravenous fluid did not have an impact on the outcome in the SAFE trial,[13] and starch solutions are not routinely used by any of the participating centres. There is no strong evidence in favour of any particular vasopressor or antihypertensive in this setting. All sites support the recently published donor management reviews,[14-16] and are expected to generally use such therapies based on current recommendations. However, while usual care will be evidence based, it will not be protocolised across the trial, but will rather reflect the care currently being provided at sites.

Outcomes

Our primary end point is the number of organs transplanted per donor.

Secondary end points include:

- the number of organs transplantable, defined as the number of organs procured but including those discarded due to factors not directly influencing their quality (such as ABO blood type or size incompatibility)
- the observed (O) versus expected (E) organs transplanted (O/E) ratio
- the 6mHFS time in recipients, defined as recipient survival after discharge from the hospital following index hospitalisation for transplantation in the first 6 months (6mHFS = days alive up to 180 – days of hospital length-of-stay)
- the relationship between plasma IL-6 concentrations in the donor and the primary and secondary end points
- the relationship between volume responsiveness (as measured by PPV) and plasma IL-6 concentrations in the donor.

Statistical analysis

Sample size and power

We want to detect a clinically important difference, and we have determined through consensus among the investigators that a half-organ absolute increase in organs per donor would be clinically relevant, as it represents a 16% increase in organs used. Currently, the number of organs transplanted from each DNDD across participating sites is about 3.1 organs, varying by donation service area from 2.28 to 3.37.[1] Using an alpha of 0.05 and a beta of 0.80, increasing organ use from 3.1 (SD, 2.5) to 3.6 (SD, 2.8) requires 443 donors per group.

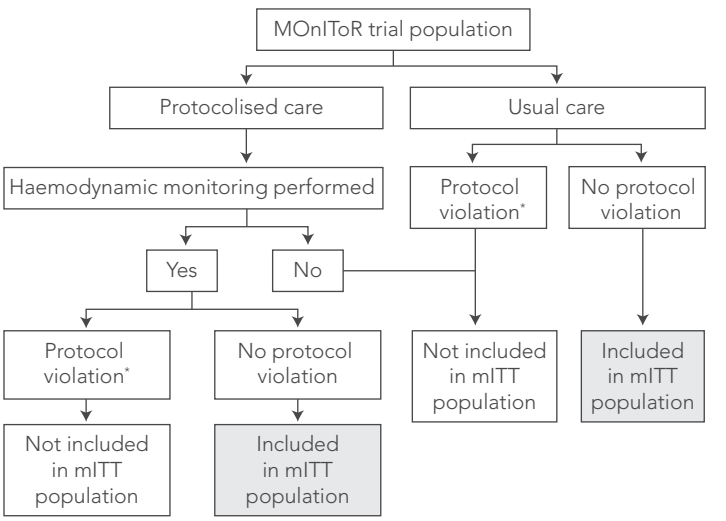
We anticipate few missing data on the primary outcome, but we have increased our planned sample size to 480 donors per group to allow for missing data. We have set the standard deviation for organ use quite high, to be conservative and because we anticipate increased variability related to use of DNDD donors via both standard and extended donor criteria. Assuming that the DNDD donors will contribute 3.0 organs transplanted per donor, we will have at least 2500 unique recipients available for the secondary data analysis. If the survival time for recipients in the usual-care group is assumed to follow an exponential distribution with median survival time of 2.5 years (87% will still be alive at 6 months), a total of 2500 recipients will give us at least 80% power to detect a minimum hazard ratio of 1.4, using a two-sided log-rank test with an alpha of 0.05.

Primary and modified intention-to-treat analyses

The trial is designed to test the primary hypothesis (that protocolised resuscitation is superior to usual care). We will conduct the primary analysis as an intent-to-treat (ITT) analysis of the mean number of organs transplanted per donor in each group, with one interim analysis and a final analysis. However, a major concern for device trials is that some subjects will not be able to receive the intervention because of problems related to the device or its use; problems outside the control of the OPCs. We are particularly concerned about this issue in this trial because the monitor has to communicate with hospital monitors, and malfunctioning or incompatible cables or other technical or logistical issues may preclude delivering the intervention. There is emerging literature on evaluating complex interventions,[17-22] and a complete discussion is beyond the scope of this paper. However, we considered whether our primary analysis should exclude patients for whom the intervention could not be delivered for reasons other than the condition of the patient. We decided to retain a strict ITT analysis as the primary analysis, and have a modified ITT (mITT) as a secondary analysis. Figure 2 shows the algorithm for patient inclusion in the mITT analysis.

Figure 2. Modified intention-to-treat (mITT) trial population

All MOnIToR subjects randomly allocated to protocolised care or usual care were considered for mITT. In the protocolised care arm, all subjects who had haemodynamic monitoring and no protocol violation were included in the mITT population. In the usual care arm, subjects without protocol violation were included in the mITT population.



MOnIToR = Monitoring Organ Donors to Improve Transplantation Results. * Protocol violation was defined as: subjects not meeting inclusion criteria but enrolled in the study and randomly allocated; subjects in the intervention arm who did not receive haemodynamic monitoring; subjects in the usual care arm who received any form of functional haemodynamic monitoring; or haemodynamic algorithm not followed by the organ procurement coordinators in the intervention arm.

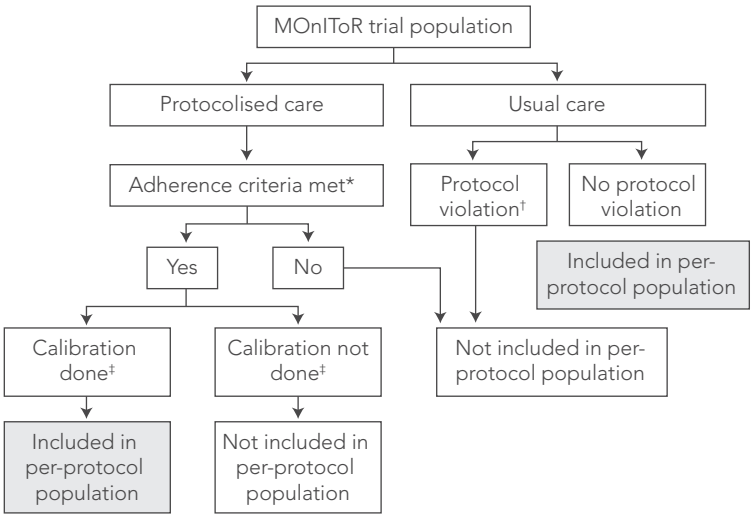
Secondary analyses

It is conceivable that some patients (even those analysed using mITT analysis) do not fully receive the intervention as the protocol indicates. For example, some patients might be withdrawn from active management for varying reasons after the intervention is begun. Although we do not anticipate this, it is conceivable that a patient could be accidentally crossed over from intervention to control or (less likely) from control to intervention. We intend to conduct a per-protocol analysis to explore potential effects of the intervention in these scenarios. Figure 3 shows the algorithm for per-protocol population.

Although our primary outcome is the total number of organs transplanted in the intervention group compared with the control group, we will also explore whether the intervention has an effect on the observed versus expected organs transplanted (O/E) ratio. The Scientific Registry of Transplant Recipients (SRTR) provides a quality metric tool (a calculator) to compare actual organ donor

Figure 3. MOnIToR trial per-protocol population

All subjects randomly allocated to either protocolised care or usual care were considered for the per-protocol population. In the protocolised care arm, all subjects for whom adherence criteria were met and the monitor was calibrated prior to use were included in the per-protocol population. All subjects in the usual care arm without protocol deviations were included in the per-protocol population.



Monitoring Organ Donors to Improve Transplantation Results * Adherence criteria were defined a priori and will be adjudicated by three study investigators. † Protocol violation was defined as subjects in the usual care arm who received functional haemodynamic monitoring. *‡ Monitor calibration was performed before initiation of the study protocol in the intervention arm.

yield against expected organ donor yield. It is based on cumulative national data analysis which integrates donor characteristics, including donor type (extended criteria and standard criteria) and donor demographics (clinical comorbidities and lifestyle information).[23] The O/E ratio is a single number that can be interpreted as follows:

- O/E ratio = 1: observed yield is the same as expected yield.
- O/E ratio < 1: observed yield is lower than expected.
- O/E ratio > 1: observed yield is higher than expected.

Interim analysis and stopping rules

A single interim analysis will be conducted after enrolling 50% (480) of the planned number of patients. We will conduct a limited set of descriptive statistics to assess similarity of groups at baseline and a primary test of the hypothesis to determine whether the study should be terminated early. The primary test is the O'Brien–Fleming test, a group-sequential test of differences between two groups that adjusts for multiple looks. We will use this test to compare differences between the two groups in mean numbers of organs transplanted. Results of these analyses will be forwarded to the steering committee, which will review and interpret the results in light of the formal O'Brien–Fleming stopping rules.

Trial management

Site training

All OPCs were required to complete a 60-minute web-based training program that reviewed the key components of the protocol and its use. Training for new coordinators was mandated for them to participate in the study. A tutorial was also made available as an educational resource throughout the study via the study website, and repeat site trainings occurred as necessary. A list of trained providers has been maintained at site level and centrally at the coordinating centre to ensure that the protocol is delivered only by trained providers. A quality assurance program was also implemented to test the recall of coordinators about properly following the study algorithm and protocol.

The members of our steering committee (comprising many of the original planning committee members [see Appendix]), have responsibility for guiding the OPO members from their regions throughout the study planning and enrolment period.

Protocol adherence

Adherence audits are being performed by three physician-investigators (J K, A A and R M) for all subjects in the intervention arm by analysing the haemodynamic data captured by the LiDCO device. All haemodynamic data graphs are reviewed independently, with investigators remaining blinded to any outcome data, and final determination of adherence is made by majority rule.

Data collection and management

Most data required for our analysis is already collected by each OPO. These data variables are entered by the OPCs into the UNOS DonorNet website, and we have permission to obtain all these data. Data regarding the organ recipients will be obtained from the SRTR.

Data and safety monitoring

OPCs report all deviations from the study protocol (including algorithm deviations), monitor-related problems, laboratory collection-related problems and any adverse clinical events. If the event pertains to LiDCO calibration issues or algorithm treatment questions, the OPCs are instructed to call the hotline to speak to an investigator for assistance. OPCs are instructed to log all events and the actions taken in response to the event via the study website at their earliest convenience. In addition, we have established an external advisory committee (see Appendix) that functions similarly to a data

and safety monitoring board. The advisory committee meets at least annually or more often, as appropriate, and meetings are timed so that reports can be considered promptly at the next steering committee meeting. Some routine meetings are held by teleconference.

Discussion

Four of the many aspects of the MOnIToR trial bear specific mention as they represent uncommon, if not unique, challenges in clinical trial design and conduct. First, virtually all biomedical research conducted within hospitals is carried out by investigative teams residing in, or closely affiliated with, the hospitals. Although OPOs are clearly working closely with hospitals, they are independent, outside entities and have to operate across many different hospitals, from small to large and academic to community-based. Adapting a trial protocol to these varied and complex environments poses a significant challenge to researchers, so we settled on a pragmatic study design that sought to influence only a very specific part of the management of donors and to limit data collection to elements being collected for organ donation purposes.

Second, studies of non-living research subjects pose interesting ethical and societal questions.[24-27] Participation in the MOnIToR trial was predicated on eligibility for organ donation, so consent for research occurred after or at the same time as consent for donation. For some OPOs, consent is bundled; for others, specific consent for the trial is sought from the subject's next of kin or legal representative. In some states, consent for organ donation is elected by the individual and is recorded on their driver's license. In all cases, family wishes concerning participation in the trial are honoured. Because the subjects in the trial were already dead at the time of enrolment, most IRBs did not view this research as in their jurisdiction, but this was not a universal opinion. Several years before our trial, the University of Pittsburgh established a separate mechanism (CORID) for review of protocols with non-living human subjects. CORID provides oversight for our trial in cooperation with local IRBs, when requested.

Third, trials of interventions in organ donors are not common. Our choice of primary end point is debatable. The goal of increasing the number of available organs from each donor is very reasonable, but many other factors influence the potential for an organ to be used. As secondary end points, we will examine usability of each organ (although no universal standard exists) and observed versus expected number of organs transplanted from each donor. This last measure may be the most objective. We will also examine the outcome in recipients, although this relationship is clearly even more complex. Finally, although the ITT analysis is usually considered the gold standard in clinical trials, there is a good rationale to consider an mITT analysis in a trial of this nature.

The MOnIToR trial is the largest randomised controlled trial conducted in the field of organ donation to date, and the results will be a significant contribution to the field.

Competing interests

None declared.

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Appendix. Monitoring Organ Donors to Improve Transplantation Results trial personnel, sites, funding and registration

Principals: Principal investigator: John A Kellum, MD; coprincipal investigator: Ali Al-Khafaji, MD, MPH; Statistician: Abdus Wahed, PhD; coordinating centre faculty: John A Kellum, MD; Ali Al-Khafaji, MD, MPH; Raghavan Murugan, MD; Abdus Wahed, PhD; coordinating centre staff: Michele Elder, RN, BSN; Ali Smith, BA; Melinda Carter, BS; Michael Willochell; Kyle Landis, BS; Qian Hao, MS.

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Steering committee: Ali Al-Khafaji, MD, MPH, University of Pittsburgh; John Kellum, MD, University of Pittsburgh; Dan Lebovitz, MD, Lifebanc, Cleveland; Raghavan Murugan, MD, University of Pittsburgh; Michael Souter, MD, University of Washington, Seattle; Susan Stuart, RN, MPM, CORE, Pittsburgh; Abdus Wahed, PhD, University of Pittsburgh.

External advisory committee: Rupert Pearse, MD (Chair), Barts and London School of Medicine and Dentistry; Luis Angel, MD, University of Texas; Howard Rockette, PhD, University of Pittsburgh.

Enrolment sites: Center for Organ Recovery and Education, Pittsburgh, PA; Lifebanc, Cleveland, OH; LifeCenter Northwest, Bellevue, WA; Lifeline of Ohio, Columbus, OH; Lifelink of Georgia, Norcross, GA; LifeShare of Oklahoma, Oklahoma City, OK; Southwest Transplant Alliance, Dallas, TX; Tennessee Donor Services, Knoxville, TN.

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Registration: Clinicaltrials.gov NCT00987714