

Special Article

Challenges to Research and Innovation to Optimize Deceased Donor Organ Quality and Quantity

P. L. Abt¹, C. L. Marsh², T. B. Dunn³,
W. R. Hewitt⁴, J. R. Rodrigue⁵,
J. M. Ham⁶ and S. Feng^{7,*}

¹Division of Transplantation, Department of Surgery,
Hospital of the University of Pennsylvania, Philadelphia, PA

²Scripps Center for Organ Transplantation, Scripps Clinic
and Green Hospital, La Jolla, CA

³Division of Transplantation, Department of Surgery,
University of Minnesota, Minneapolis, MN

⁴Division of Transplant Surgery, Mayo Clinic, Phoenix, AZ

⁵Departments of Psychiatry and Surgery, Center for
Transplant Outcomes and Quality Improvement, Beth
Israel Deaconess Medical Center, Boston, MA

⁶Division of Abdominal Organ Transplantation, Department
of Surgery, University of Nevada School of Medicine, Las
Vegas, NV

⁷Division of Transplantation, Department of Surgery,
University of California, San Francisco, CA

*Corresponding author: Sandy Feng,
sandy.feng@ucsfmedctr.org

Solid organ transplantation is encumbered by an increasing number of waitlisted patients unrequited by the current organ supply. Preclinical models suggest that advances in deceased donor management and treatment can increase the quantity and quality of organs available for transplantation. However, the science of donor intervention and the execution of high quality, prospective, multi-center, randomized-controlled trials are restricted by a myriad of logistical challenges mired in regulatory and ethical ambiguity. By highlighting the obstacles to conducting research in deceased donors, this report endeavors to stimulate the creation of a multi-disciplinary framework to facilitate the design, implementation and supervision of innovative trials that increase the quantity and/or quality of deceased donor organs.

Key words: Consent, deceased donor, donor management research, kidney transplantation, liver transplantation, next-of-kin

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Background

Since the first successful renal transplant in 1954, the field of solid organ transplantation has been notable for

improving outcomes. This success has been driven by advances in diverse areas such as immunosuppression, surgical technique, critical care and antimicrobial therapy. Today, transplant recipients can expect 5 year survival rates exceeding 70% (1). To some extent, transplantation is a victim of its own success, with over 100 000 patients currently waiting for an organ in the United States. This number greatly exceeds supply, resulting in prolonged waiting times and an unremitted risk of waitlist morbidity and mortality. To alleviate this disparity, the donation and transplantation community has promulgated deceased donation through a series of breakthrough collaboratives. By identifying and implementing best practices and establishing goals for organ procurement, a marked increase in the number of organs available for transplant has been realized (2). Despite these initiatives, deceased donation remains inadequate to serve the increasing number of transplant candidates.

Hypothetically, advances in donor management through a variety of interventions may increase the quantity and quality of the current organ supply and thereby enhance both transplantation opportunities and outcomes. However, the clinical science of treating donors to improve posttransplant organ function remains relatively underdeveloped, particularly considering the rich fabric of basic science discovery in ischemia/reperfusion injury. The paucity of rigorous research in this arena attests to a need to aggressively advance the science of donor treatment to ensure that the decedent's donation intentions are followed, increase the number of transplantable organs, reduce disease burden and lower waitlist mortality.

A review of the medical literature and www.clinicaltrials.gov evidences a sparse number of donor intervention trials (3). Dominant themes are interventions that investigate current concepts of ischemia/reperfusion injury utilizing either standard approaches such as ischemic preconditioning and tight glycemic control or common pharmaceuticals such as corticosteroids and dopamine (4). The plethora of molecular pathways described in preclinical models, exemplified by inhibition of apoptosis, induction of hemoxygnase-1 and inhibition of complement, remain largely unexplored. The design, organization and execution of high quality, prospective, randomized controlled trials in deceased donors are severely curtailed by a myriad of ethical and logistical challenges. Significant uncertainties are engendered by the absence of guidelines for consent in

donor-based research, of federal regulations governing research in deceased human subjects, and of mechanisms to notify recipients and recipient transplant physicians about donor research trials. This report highlights the numerous obstacles to innovation and research in deceased organ donation and transplantation within the United States; which may not pertain to the legal and ethical framework of organ donation and transplantation in other countries. By raising awareness regarding the extent and complexity of the issues, we aim to motivate a comprehensive and multi-disciplinary approach to formulate guiding principles for the design, execution and oversight of high quality clinical trials to increase both the quality and quantity of deceased donor organs available for transplantation.

Consent

Donors: Authorization

An essential element of any study is that it be conducted in an ethical manner, with transparency and equipoise for participants. Deceased donor intervention trials are unique in that “participants” can include not only the donors themselves but also donor families, waitlist candidates and organ recipients. The necessity of informed consent for participation in a study among these multiple parties remains ambiguous, clouded by ethical uncertainty and a lack of regulatory and legal structure (5–7).

With respect to deceased donors, it is important to differentiate “authorization” for organ donation from informed consent, for different legal foundations govern these two acts. The law views deceased organ donation whether for transplantation research or education, as anatomical gifting and not as medical decision-making that requires informed consent (8). In every state, permission for organ donation derives from adoption of the Uniform Anatomical Gift Act (UAGA), which is expressly based on gift law. Mechanisms for designating oneself as an organ donor before death include authorization in an advanced directive or through a state registry, referred to as a Donor Designation. Uniformity does not exist among state registries with regard to clarifying the use of the anatomical gift for transplantation or research. In states where registry designation solely authorizes transplantation, deceased donor-based research may require separate permission from the next of kin. This state-by-state variation as to whether Donor Designation includes permission for research highlights the complexities and ambiguities regarding proper authorization for research in deceased organ donors.

Given extant laws and legal doctrine, the elements of informed consent that generally govern deliberations in living research subjects do not apply to deceased research subjects. However, the intent of informed consent is to protect the individual from harm and to promote dignity and autonomy. While research cannot inflict true harm on a

deceased organ donor, research can compromise the donor and donor family intention to benefit society with their gift. In this context, despite the intention to improve donor organs, research can potentially injure them, thereby compromising transplantability or diminishing posttransplant outcomes and running counter to the wishes of the donor and the donor family. This has led some to support surrogate informed consent for deceased donor participation in clinical trials (9). Confusion with regard to the necessity of donor consent is evidenced by variable use of proxy consent among published donor management trials (10–14). Despite this ambiguity, donor-based research must respect the wishes of the decedent so that organs intended for transplantation are sufficiently protected against injury through the unintentional consequences of a study protocol.

The federal Office for Human Research Protection (OHRP), which oversees Institutional Review Boards (IRBs) under federal regulation 45 CFR 46, does not regulate research involving the deceased. However, research occurring in donation after cardiac death donors prior to declaration of death would fall under the auspices of an IRB, reducing some of the ambiguity incurred when considering research in the deceased. Although not legally required, absence of an IRB requirement for deceased donor research has created a regulatory vacuum with confusion among investigators, organ procurement organizations (OPOs), donor hospitals and their IRBs. While many OPOs have biomedical review boards that govern research activities, the processes for evaluating and overseeing donor-based clinical trials are inconsistent. The extent of formal IRB involvement in deceased donor studies is variable among both OPOs and donor hospitals, running the gamut from qualification for exempt status to full IRB oversight. Although the federal government does not place oversight of donor research in the hands of IRBs, donor hospitals have substantial legal and financial interests that motivate some degree of oversight in the setting of an undefined ethical and legal risk.

Waitlist candidates and transplant recipients: Informed consent

Donor intervention and treatment studies pose risk to both waitlist candidates and transplant recipients. A waitlist candidate offered an organ that has been exposed to an intervention might decline the organ specifically as a result of that intervention, delaying transplantation and possibly increasing waitlist morbidity or even mortality.

Candidates who choose to accept organs previously exposed to innovative treatments will be directly exposed to the risk of the intervention. However the process and standards for consent of transplant recipients pose unique challenges. Published randomized controlled donor studies fail to provide guidance as recipient consent is rarely addressed (10–13). The need for consent depends on whether a recipient is considered a human research subject

under federal regulations; that is whether the study investigator obtains data through an intervention or interaction with the recipient or obtains identifiable information about the recipient for research purposes. If no recipient data is gathered, for example in a study aimed to identify a biomarker of inflammation in the donor, recipient consent may be unnecessary. However, in such a scenario, if donor or organ treatment could pose a risk to the recipient's outcome, requirement for recipient consent is ambiguous. If the recipient is considered a research subject, studies determined by an IRB to present minimal risk may receive a prospective consent waiver if: 1) the research cannot be practically carried out without a waiver and 2) waiving consent will not adversely affect the rights of the participants (9). Studies posing higher than minimal perceived risk may, however, merit full informed consent.

Consent in transplant candidates/recipients entail two discrete issues; 1) acceptance of the organ and 2) participation in the study. Any informed consent process for a recipient should include information about the intervention as well as the potential risks to the recipient from accepting, or declining, the organ. The transplant candidate would also need to be informed about the protocol for specimen and/or data collection after transplantation. The United Network of Organ Sharing currently collects patient and graft survival and, to some extent, organ function data through agreements with transplant centers that are not subject to recipient consent. However, it remains to be determined whether this data could be used to identify individual patient outcomes. More granular recipient data would certainly require recipient informed consent and IRB approval. Inherent to any donor intervention trial, study participation by the transplant candidate or recipient should never be considered a prerequisite to and must be separated from organ acceptance and transplantation.

Donor and Recipient Hospitals

Donor intervention studies have broad implications for both donor and recipient hospitals. The majority of interventions take place at the donor hospital; as such each and every hospital has the potential to have a donor in a study protocol. Among the more than 5,000 hospitals in the United States, most lack policies regarding the regulation and oversight of clinical trials involving deceased organ donors. However, in hospitals where donor intervention has occurred, oversight processes have been highly variable, ranging from nonexistent to administrative approval from an ethics or staff review panel to full IRB approval. OPOs and hospital administrators generally confirm that some level of donor hospital-based approval should be secured. Donor hospitals have an interest in interventions performed in deceased patients, given their relationship with the community that they serve. Addition-

ally, an erosion of public trust in the donor hospital secondary to a lack of transparency or oversight could be deleterious for organ donation. The absence of policy and lack of standardization among donor hospitals pose a monumental logistic and administrative challenge to investigators. The approval process for a study protocol borders on insurmountable when one considers that investigators must navigate a protocol through individual donor hospitals, most without established policies, to construct a multi-center donor intervention study. A clear pathway for the approval of donor intervention study protocols by individual hospitals must be delineated.

Similarly, donor intervention studies impose heightened risks to recipient hospitals and their transplant programs. Two scenarios illustrate the potential negative aspects of a donor intervention trial to a recipient center: 1) declining an organ from a research donor for a candidate who subsequently becomes too ill for transplantation or dies or 2) suboptimal transplant outcome attributable to a donor intervention under study. Few if any areas of medicine receive the degree of federal and state regulation as well as public scrutiny as transplantation. A diverse array of data related to each and every program's waitlist and posttransplant outcomes are publicly available. Transplant programs and their associated hospitals potentially risk volume contraction, accreditation, insurance contracts and revenue shortfalls if waitlist or posttransplant outcomes suffer as a result of declining or accepting study organs with uncertain outcomes.

Communications and Allocation

Organ allocation and distribution in the United States is based upon a structured system governed by rules established by the OPTN and UNOS. Communication and implicit trust between OPO donor coordinators, donor surgeons and recipient physicians are fundamental. Failure to provide detailed information about donor intervention will compromise the integrity of the allocation system. The transplant surgeon/physician must have sufficient information about the research to conduct his/her own risk-benefit assessment regarding the acceptance or declination of the organ for the intended recipient. Importantly, to meet the essential elements of informed consent, the transplant surgeon/physician should be able to provide the intended recipient with study details and answer questions that the patient may have. However, no mechanism currently exists to convey information to a transplant physician or candidate about the rationale and/or the specifics of a research intervention in a deceased donor. The establishment of a central repository to list donor-based studies with standard, well-defined descriptive elements that is linked to or integrated with UNet, the secure internet-based program used for dissemination of donor information and organ allocation should be considered.

Donor intervention studies may complicate or alter existing organ allocation pathways via several mechanisms. Illustrative scenarios include:

- 1) Organs exposed to an intervention may be (unexpectedly) allocated to a recipient whose transplant center is not involved in and unaware of the study, complicating decision-making by the recipient physician regarding organ acceptance or declination and the investigator's ability to collect specimens and/or data to assess the intervention.
- 2) Organs from high risk studies may be preferentially declined for specific patient subsets, such as those with high disease severity or those in regions with shorter waiting times, thus shifting the risk burden within the allocation paradigm.

In these and other scenarios, it is likely that organ allocation, distribution and utilization will be variably influenced as a function of the number of enrolled donors. Monitoring the impact of donor-based studies on organ allocation and distribution should be undertaken.

Oversight

As the previous sections have illustrated, there are few guidelines, limited oversight and an absence of well-considered algorithms to carry out donor intervention or treatment research. The uniqueness and complexity of these studies locate them outside of existing regulatory structures. The development of a framework to ensure centralized organizational and oversight mechanisms is required. A variety of study-related components such as protocol approval from donor and recipient hospitals, dissemination of study information and safety monitoring may be best handled in a centralized and coordinated manner. A centralized mechanism will also facilitate the comprehensive assessment of an intervention's impact across all exposed organs. In a trial where an intervention is being tested to have a specific outcome in only one organ, any detrimental impact on the allocation, distribution and/or function of the other organs or the outcomes of their recipients should be monitored and assessed. A centralized review and oversight process with regional or national jurisdiction would be best able to determine equipoise and ensure that the intended gifts are honored appropriately.

Conclusion

Innovation and research in deceased donor management and treatment has the potential to substantially increase both the quantity and quality of organs available for transplantation and thus mitigate waitlist mortality and improve posttransplant outcomes. A plethora of intervention strategies exist, as suggested by the wealth of basic

science discoveries in the physiologic and immunologic consequences of brain death as well as ischemia/reperfusion injury. However, innovation remains stifled in the setting of ethical, logistical and regulatory barriers at multiple levels. A concerted and coordinated effort among overlapping government agencies led by the US Department of Health and Human Services, working closely with members of the organ donation and transplantation community, is essential to comprehensively address the issues and thereby ensure the safe and optimal design of clinical trials in deceased donation and transplantation.

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Disclosure

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