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CLINICAL INVESTIGATION

Perspectives on Deceased Donor Intervention Research—Opportunities and the Imperative for Continued Progress

KEYWORDS: deceased donor intervention research; ethics; normothermic regional perfusion; regulations

Michael Kueht, MD[1]
Madhukar S. Patel, MD, MBA, ScM[2]
Ali Zarrinpar, MD, PhD[3]
on behalf of the American Society of Transplant Surgeons Donor Research Policy & Advocacy Task Force

THE CHALLENGE

The field of critical care medicine is intrinsically linked to the success of organ transplantation, as critical care providers play a pivotal role in managing potential organ donors. Advances in transplantation, from organ preservation to donor-recipient matching, has been marked by groundbreaking research involving deceased donors. However, ethical, legal, and regulatory challenges in deceased donor intervention research (DDIR) have stymied progress and threatens the quality and quantity of organs available for transplantation (1–4). For clarity, DDIR relates only to interventions that occur after death determination. Specifically, for donors declared dead by circulatory criteria, DDIR applies to research conducted after the declaration of death. Any intervention conducted prior to the declaration of death is performed on a living human being and requires consent from the donor or an appropriate representative, as the recipient is not involved in pre-mortem interventions.

The history of DDIR illustrates the inconsistent reception of such studies by regulatory bodies and the public. A landmark multisite randomized controlled trial (RCT) conducted in 1992 at the University of Leiden demonstrated the superiority of the preservation solution (University of Wisconsin-Belzer solution) over EuroCollins in the occurence rate of delayed graft function (DGF) and graft survival after kidney transplantation, leading to widespread acclaim, changing the standard-of-care (5). Conversely, a 2015 RCT published in the *New England Journal of Medicine* by Niemann et al (6) assessing the impact of donor hypothermia on DGF faced significant criticism for its consent process, specifically regarding whether the true research subjects were the donors or recipients. Despite subsequent studies on donor hypothermia being conducted without similar controversy, the lingering concerns from earlier criticisms have dissuaded many investigators from pursuing interventional studies in this domain (7, 8). Identifying the research participants is and will likely remain an issue for DDIR given that there are implications for the donor and family, recipients of targeted organs, and recipients of nontargeted organs and tissue.

Instead, researchers have increasingly turned to observational approaches. For instance, studies led by Patel et al (9) and Malinoski et al (10) involving multiple organ procurement organizations (OPOs) and transplant centers have

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shown the benefits of actively pursuing prespecified donor management goals on organ yield and function. This has resulted in significant improvements in the number and quality of transplantable organs through specific protocoled interventions in donor management, although the practices have yet to be uniformly implemented.

Indeed, many interventions currently implemented as part of routine critical care are aimed at optimizing transplant outcomes (e.g., sodium management, mechanical ventilation recruitment maneuvers, etc.), even though they have not been yet subjected to rigorous trials. These interventions are nontherapeutic for the donor, but they can benefit recipients, and in doing so maximize the likelihood of honoring a donor's wish for successful donation. While consent is not obtained for these interventions when they are part of a clinical protocol, it would be necessary if they were studied in research contexts. Ethical guidance on this kind of research is important and could be guided by experience gained from a Donor Research Oversight Committee (DROC) and single Institutional Review Board (sIRB) (11).

To advance the care of end-stage disease patients and expand the donor pool, it is essential to revitalize DDIR. Addressing the ethical and regulatory complexities requires collaborative efforts among federal agencies to harmonize regulations and establish robust ethical and legal frameworks. Proposals include the creation of a centralized Institutional Review Board, a DROC, and a Data Safety Monitoring Board (DSMB) to provide consistent oversight. Drawing inspiration from successful national models like the National Liver Review Board, these initiatives could streamline processes and ensure that both donor dignity and recipient welfare remain at the forefront of research priorities. These measures could allow those involved in the care of the critically ill to implement standardized practices that could improve outcomes across the board.

WHAT ARE WE MISSING OUT ON WITHOUT DDIR?

DDIR affords the opportunity for in situ interventions on organs after declaration of death, but while organs remain in the donor. Potential benefits are manifold and range from mitigating organ damage through targeted and generalized early interventions to organ conditioning and repair. Possible domains of research hold promise for increasing the number and quality of organs for transplantation (**Fig. 1**).

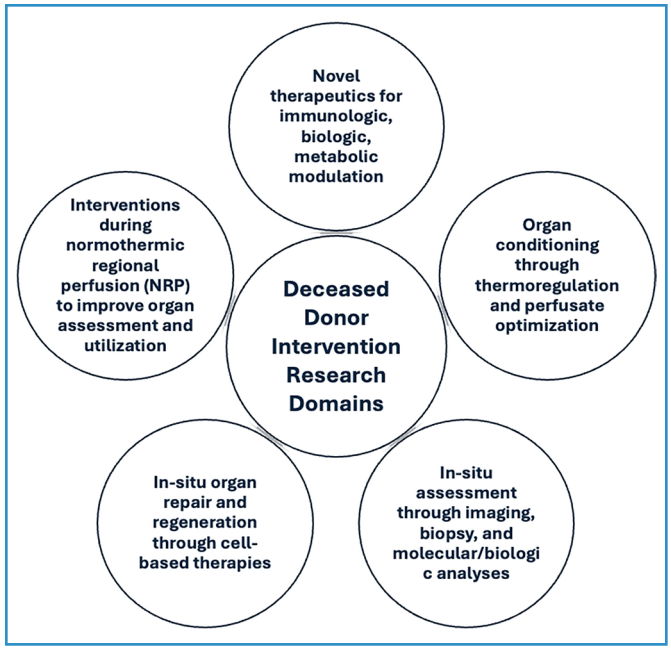

Figure 1. Overview of deceased donor intervention research (DDIR) domains. This figure provides a comprehensive categorization of the key research areas within DDIR. It highlights the central focus on improving donor organ viability and transplant outcomes through novel therapeutics, organ conditioning, in situ assessment, in situ organ repair and regeneration, and normothermic regional perfusion (NRP). Each domain represents a critical area for advancing transplantation science and enhancing the quality of organs available for transplantation.

Novel Therapeutics for Immunologic, Biologic, and Metabolic Modulation

In situ interventions enable delivery of drugs or therapeutic agents directly to the target organ or more broadly, including agents to mitigate ischemia-reperfusion injury, reduce inflammation, or modulate the organs' immune profile to reduce the risk of rejection.

Organ Conditioning Through Thermoregulation and Perfusate Optimization

Techniques such as controlled oxygenated rewarming or localized hypothermic perfusion can be employed in situ to condition organs, especially those deemed marginal. This, as well as improved perfusate solutions, could recondition organs, enhancing their resilience and function post-transplant.

In Situ Assessment Through Imaging, Biopsy, and Molecular/Biologic Analyses

Beyond interventions, in situ studies can provide insights into organ health and function. Real-time assessments using imaging modalities, biopsies, or biologic/molecular analyses can improve understanding of the organ's state while in the donor, guiding decisions on suitability for transplantation in appropriately matched recipients.

In Situ Organ Repair and Regeneration Through Cell-Based Therapies

The potential to repair organs, using techniques like stem cell infusion or tissue engineering, could be transformative. For donors who have experienced traumatic or significant biologic events or for organs with localized damage, in situ repair could salvage organs that would otherwise be discarded.

Interventions During Normothermic Regional Perfusion

Normothermic regional perfusion (NRP) involves in situ perfusion of specific organs or regions within the deceased donor's body. By restoring organs to a near-physiologic state, NRP can help correct the derangements that accumulate there during the dying process in donors after death determination using circulatory criteria. The incorporation of various interventions during NRP can further enhance organ viability and increase the number of organs suitable for transplantation.

REGULATORY CONSIDERATIONS

Clinical trials involving organ donors fall under the purview of multiple federal agencies, each with their own regulations (**Fig. 2**). The Health Resources & Services Administration, for instance, oversees the equitable allocation of organs. The U.S. Department of Health and Human Services (HHS), through the Office for Human Research Protections, ensures the protection of human subjects in research, while the U.S. Food and Drug Administration regulates the safety and efficacy of drugs and devices. Navigating this regulatory landscape requires understanding each agency's mandate and a proactive approach to compliance.

The primary issue is the absence of a regulatory pathway for waiver of informed consent for DDIR studies that pose more than minimal risk to transplant recipients. Obtaining informed consent from recipients is often not feasible due to several reasons: organ procurements frequently occur with the specific recipients unknown at the time of the operation; the transplantation process is marked by great urgency; and recipients and physicians must make expeditious decisions about organ acceptance. Specific factors impeding informed consent under regulation 45 Code of Federal Regulations (CFR) 46 include severe time constraints in most cases leaving no time for recipients to discuss and consider participation, a lack of comprehensive knowledge about the research project (and potentially multiple research projects) among those interacting with recipients, and the need to manage organs as a scarce resource for public good. Except for emergency research in life-threatening situations, only minimal risk research (45 CFR 46.116(f)(3)) is currently allowed a waiver. Although the dilemma of which stakeholders require informed consent (donor/family, recipients of targeted organs, recipients of nontargeted organs and tissue) remains, current donor management practices influenced by low quality evidence, have the same potential for negative impact.

To address these challenges, HHS could consider two main options: amending existing regulations to establish a waiver pathway for DDIR (Rulemaking) and creating a waiver under 45 CFR 46.101(i) ("Secretarial waiver"). The latter option allows for the waiver of some or all provisions of 45 CFR 46, provided that the alternative procedures align with the Belmont Report's principles of justice, autonomy, and beneficence. Other potential consent models, such as integrated and deferred consent, and alternative models like providing prior information about ongoing trials to recipients awaiting transplantation can be considered. We propose an interdisciplinary analysis and the development of a comprehensive donor intervention consent framework involving relevant stakeholders, including donation and critical care professionals, transplant surgeons and physicians, clinical research ethicists, and donor family and recipient partners. Also, although applying international experiences can be complicated by the different regulatory frameworks in each country, international consultation can still be valuable—particularly

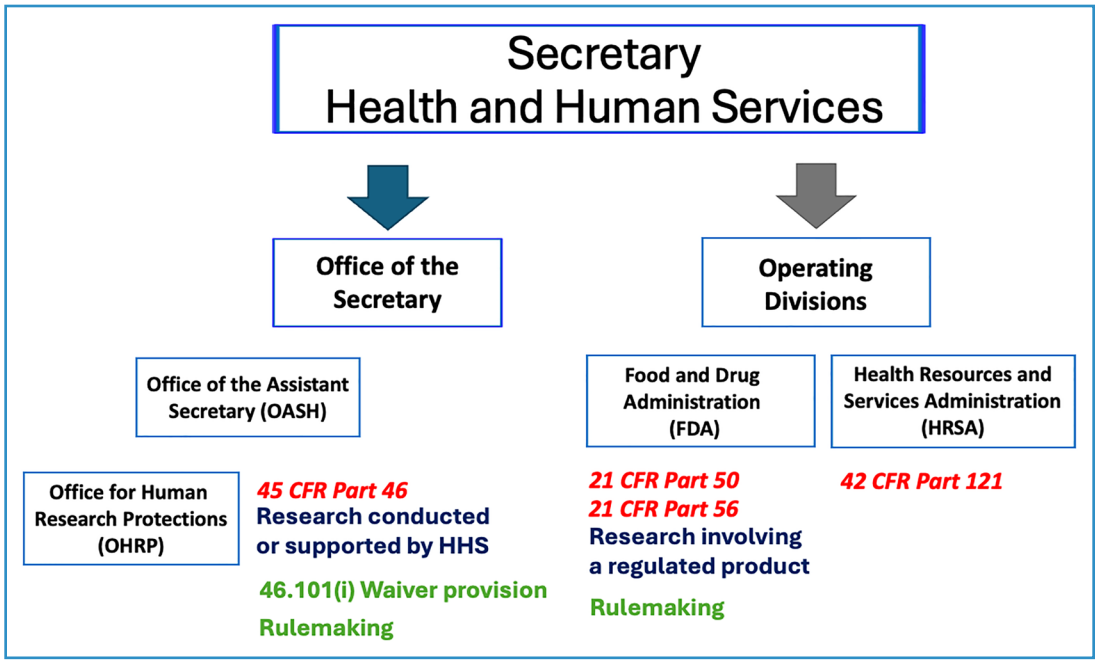

Figure 2. An overview of the organizational structure of the Secretary of Health and Human Services (HHS). This flowchart illustrates the various federal agencies and their specific regulatory responsibilities related to deceased donor intervention research. It includes the Office for Human Research Protections (OHRP), governed by 45 Code of Federal Regulations (CFR) Part 46, which covers research conducted or supported by HHS, including waiver provisions (46.101(i)). The Food and Drug Administration (FDA), under 21 CFR Parts 50 and 56, regulates research involving regulated products and rulemaking. The Health Resources and Services Administration (HRSA), under 42 CFR Part 121, oversees the equitable allocation of organs. Each agency has distinct responsibilities, emphasizing the complexity and the need for coordinated oversight within the regulatory landscape. OASH = Office of the Assistant Secretary for Health.

for learning about the integration of donor families and donation experts into DDIR processes. The proposed national review board may determine the appropriate type of consent for various situations, ensuring a balanced and ethically sound approach.

PROPOSAL

The current impasse in donor research is undeniably complex, but it is not insurmountable. By fostering collaboration among OPOs, transplant clinicians, and federal agencies, and by ensuring that ethical considerations are at the forefront of all endeavors, we can pave the way for continued progress. To maintain trust in the system, incorporating viewpoints from all stakeholders, especially donor families, will be critical. Key to this is the establishment of clear guidelines that harmonize the regulations of different agencies, coupled with robust ethical frameworks that prioritize both the dignity of the donor and the well-being of the recipient.

In an effort to advance DDIR, we concur with recommendations from Secretary's Advisory Committee on Human Research Protections to establish a national centralized DROC, sIRB for DDIR, and DSMBs (12). Together they will play crucial roles in reviewing, approving, and monitoring all donor intervention trials throughout the United States. The DROC will evaluate the scientific merit and ethical compliance of these trials (including conflicts of interest), monitor the safety of waitlisted candidates and transplant recipients, and oversee the impacts on organ donation, allocation, and distribution. Inconsistently reported in previous donor trials, a crucial component of study proposals will be adverse event monitoring strategies for off-target-organ effects and organ recovery rates. The sIRB ensures consistent review standards across all institutions, while the DSMB provides ongoing safety oversight during the trials. The implementation of such oversight is essential to ensure that DDIR adheres to the highest scientific and ethical standards.

To support these activities, development of a robust information technology (IT) infrastructure is necessary, drawing on successful models from previous research trials such as the hypothermia study (7, 8). Currently, much of the infrastructure for linking deceased donor data with recipient outcomes is already in place, managed through an agreement and paid support by United Network for Organ Sharing. This system has worked well without notable challenges

or concerns regarding security, confidentiality, or accountability. Building on this existing framework, we aim to further streamline communication among transplant professionals, candidates, recipients, and the public, establishing a comprehensive framework for data management and trial monitoring. Special attention will still be needed for integrating donor and recipient data into new research initiatives. The creation of such a system is crucial for maintaining transparency and trust, facilitating the smooth operation of nationwide research initiatives. Consistent with recent changes in the organ transplant regulatory IT space, privacy and accountability will be of paramount importance at the outset.

The move from single-institution pilot studies to impactful multicenter or nationwide interventional trials necessitates the creation of national-level platforms, particularly as organ recovery centers become more central to the transplantation process. Critical care medicine physicians are integral to this evolution, given their pivotal role in managing potential donors and optimizing donor care. The success of coordinated programs like the National Liver Review Board demonstrates that nationwide collaboration across disciplines and institutions is both feasible and effective. Drawing inspiration from such models, we propose launching 1–2 pilot clinical intervention trials in partnership with the American Society of Transplant Surgeons and the American Society of Transplantation. These trials would test the feasibility of centralized oversight structures and the IT infrastructure, while also emphasizing the integral role of critical care teams in donor management and trial execution. By engaging multidisciplinary teams in these initiatives, we can enhance donor interventions and align efforts with the broader goals of the critical care and transplant communities. This collaborative framework, informed by guidelines from the National Academy of Medicine and transplant community recommendations, aims to address current barriers in DDIR and advance patient outcomes across both fields.

1 *Division of Transplant Surgery, University of Texas Medical Branch, Galveston, TX.*

2 *Division of Surgical Transplantation, UT Southwestern Medical Center, Dallas, TX.*

3 *Division of Transplantation and Hepatobiliary Surgery, University of Florida, Gainesville, FL.*

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For information regarding this article, E-mail: Ali.Zarrinpar@surgery.ufl.edu

The American Society of Transplant Surgeons Donor Research Policy & Advocacy Task Force members are listed in the ***Appendix*** *section.*

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APPENDIX

The American Society of Transplant Surgeons Donor Research Policy & Advocacy Task Force: Hannah Copeland, MD (Lutheran Hospital, Fort Wayne, IN); Raja Kandaswamy, MD, MBA (Division of Transplantation, Department of Surgery, University of Minnesota, Minneapolis, MN); Stacee Lerret, PhD, RN (Pediatric Gastroenterology, Hepatology, and Nutrition, Medical College of Wisconsin, Milwaukee, WI); Kevin Myer (LifeGift Organ Procurement Organization, Houston, TX); Claus Niemann, MD (Department of Anesthesia, School of Medicine, University of California, San Francisco, CA); Michael Nurok, MD, PhD (Department of Anesthesiology, Medical Director Cardiac Surgery ICU, Cedars-Sinai Medical Center, Los Angeles, CA); Anil S. Paramesh, MD, MBA (Abdominal Transplant, School of Medicine, Tulane University, New Orleans, LA); Elizabeth Pomfret, MD, PhD (University of Colorado School of Medicine, Aurora, CO); Cristiano Quintini, MD (Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy); Timucin Taner, MD, PhD (Division of Transplantation Surgery, Mayo Clinic, Rochester, MN); and Anji Wall, MD, PhD (Baylor Scott & White Health, Baylor University Medical Center, BSW Center for Innovation, Science, Policy Research, and Ethics, Dallas, TX). Endorsed by the American Society of Transplant Surgeons Council and the American Society of Transplantation Executive Committee.