

Editorial

Organ Donor Research: It Is Time for Much Needed Clarity

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When faced with the grim landscape of morbidity and mortality attributable to the organ shortage, the medical community intuitively looks to research for solutions. Basic discoveries vetted in the literature, followed by rigorous testing in increasingly relevant animal models, and culminating in prospective, randomized trials that prove safety and efficacy delineate the classical pathway of medical advances. While there has been considerable effort expended in the realm of basic science to explore mechanisms of organ injury during brain death and identify interventions to mitigate this injury, astonishingly little has progressed beyond an initial stage of discovery to reach the clinical arena (1).

The tantalizing potential of donor intervention research to increase the quality and possibly quantity of organs from deceased donors is emphatically illustrated by a recent publication in the *New England Journal of Medicine* (2). A randomized trial tested the hypothesis that mild hypothermia (34.0–35.0°C, n = 180) attained through noninvasive management could reduce the incidence of delayed graft function (DGF), the primary endpoint, in kidney recipients. Compared to normothermia (36.5–37.5°C, n = 190), hypothermia reduced DGF incidence (odds ratio 0.62, CI 0.43–0.92, p = 0.02). This is a most impressive result, considering the checkered history of prior attempts to address DGF, and a result that raises expectations for future investigative efforts in deceased donor research.

Donor intervention research straddles boundaries rarely encountered in traditional clinical trials, since the experimental procedure occurs in deceased donors while study outcomes are most frequently measured in the organ recipients. Ethical concerns, regulatory ambiguity, and

logistical complexity abound (3,4). Who are the research subjects—the deceased donors, the organ recipients, or both? When transplant physicians explain and discuss the research intervention as part of the donor and organ description to potential recipients, will he/she be asking for informed consent to accept the organ for transplantation, to participate in research, or both? Does the answer to this question depend on whether the recipient is receiving the organ under study (for example, the kidney recipients of a DGF study) versus receiving organs that are not under study (for example, the heart, lung, and/or liver recipients of organs from the same donor)?

For the hypothermia study, ethical and regulatory issues were transparently vetted through an inclusive process involving Institutional Review Boards (IRBs), regional transplant physicians, organ procurement organizations (OPO), and OPO research boards, as well as donor hospitals and recipient transplant centers. The simplicity and low-risk nature of the intervention mitigated the obstacles that would, without a doubt, obstruct the testing of greater risk, invasive interventions, or novel pharmacological agents. Specifically the University of California San Francisco (UCSF) IRB deemed that the clinical trial was not human subjects research as the intervention was occurring in a deceased donor. Moreover, they ruled that recipient consent was not required because hypothermia represented minimal risk to the recipient and there were neither data nor specimen collection directly from the recipient; posttransplant outcome data were collected through the Scientific Registry of Transplant Recipients in a de-identified manner.

In response to the study, Public Citizen, a nonpartisan organization, wrote a letter addressed to the Director of the Office of Human Research Protections, United States Department of Health and Human Services and the Office of Research Oversight of the Veterans Health Administration (<http://www.citizen.org/documents/2315.pdf>). The letter raised concern “that the trial, as conducted was unethical and failed to materially comply with key requirements of the Health and Human Services and Veterans Administration regulations for the protection of human subjects.” The authors raised three primary concerns: (1) The UCSF IRB, which was the lead institution, determined incorrectly that the research represented “nonhuman subjects”; (2) As a result the investigators failed to

obtain informed consent of the subjects of the trial, in violation of the basic ethical principle of respect for persons as articulated in the Belmont Report and in violation of federal requirements; (3) The UCSF IRB failed to review and approve the trial in accordance with requirements of the human subjects' protection regulations.

The claims from Public Citizen are troublesome. While a debate of the merits of the complaint is not within the scope of this editorial, the allegations have, *de facto*, stopped all future deceased donor intervention research. The letter emphatically illustrates that deceased donor research does not readily map to existing federal requirements for review and approval of human subjects' research—a vacuum requiring ethical and regulatory lucidity. If an intervention as benign as mild hypothermia, which has received IRB approval after extensive vetting, rears the specter of inadequate adherence to standards of human subjects' research, how can we construct a framework that will allow donor intervention research to move forward in an ethically responsible manner?

Two efforts are under way. The first is the initiation of a study on the ethics and implications of deceased donor intervention research by the Institute of Medicine (IOM). This distinguished organization has a record of bringing clarity and definition to other areas of organ donation and transplantation by assembling an impartial team of experts from a wide range of disciplines. The second is engagement with Health Resources and Services Administration (HRSA) by a committee representing a broad coalition of the organ donation and transplantation community to delineate a comprehensive and national oversight mechanism. As envisioned, a multidisciplinary board would have tripartite functions beginning with assessment of scientific and ethical merit, ensuring robust human subjects' protection, and culminating in

safety and impact monitoring that encompasses both waiting list candidates and all recipients of organs from donors involved in interventional research.

So where do we stand? At the present time, donor intervention research is stymied. Confusion abounds among investigators, OPOs, IRBs, and the public. The complaint from Public Citizen highlights the vacuum of ethical clarity and regulatory oversight. Ongoing efforts by the IOM and deliberations by HRSA must provide guidance. We are encouraged, but chastened by the prospect that further delays incur additional morbidity and mortality among transplant candidates and deny organ donors the opportunity to maximize their gift.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

References

1. Feng S. Donor intervention and organ preservation: Where is the science and what are the obstacles? *Am J Transplant* 2010; 10: 1155–1162.
2. Niemann CU, Feiner J, Swain S, et al. Therapeutic hypothermia in deceased organ donors and kidney-graft function. *N Engl J Med* 2015; 373: 405–414.
3. Abt PL, Marsh CL, Dunn TB, et al. Challenges to research and innovation to optimize deceased donor organ quality and quantity. *Am J Transplant* 2013; 13: 1400–1404.
4. Rodrigue JR, Feng S, Johansson AC, et al. Deceased donor intervention research: A survey of transplant surgeons, organ procurement professionals, and institutional review board members. *Am J Transplant* 2016; 16: 278–286.