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Addressing Barriers to Organ Donor Research—A Renewed Call for Regulatory Guidance

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The promise of deceased donor management research to deliver innovations that will increase the quantity and quality of organs available for transplant has captivated the collective work of many in the field. Despite this obvious path to harness clinical innovation and drive improvement, the paucity of active protocols is evidence of the continued barriers to conducting this research. In "Disparities in Deceased Organ Donor Research Authorization: Experience at One Organ Procurement Organization and Call for National Conversations,"[1] Lentine *et al*. identify that donor authorization rates vary by race and conclude that addressing this will enable research to optimize organ donation outcomes. Continuing to improve research authorization across demographic categories is a laudable goal, and, for some protocols, this is critical to the research itself, such as the National Institutes of Health–funded Apolipoprotein L1 Long-Term Outcomes (APOLLO) study underway that seeks to define the impact of APOL1 genotype on the transplantation outcomes of recipients from African American organ donors. Nonetheless, the overall research authorization rate was nearly 90% at the studied Organ Procurement Organization. This high level of research authorization raises the question of whether donor authorization is currently a significant rate-limiting factor to conducting this important research.

The most significant barriers to conducting donor management research have previously been identified as the complexities in meeting regulatory requirements for human subjects research and, in particular, the issue of transplant recipient informed consent.[2–4] Since 2015, there appears to have been only 1 or 2 active protocols at any given time across the entire field. These protocols are organ specific with defined eligibility criteria, reducing the potential pool of participants. On the one hand, this points to the need to maximize donor authorization to leverage these rare research opportunities; on the other hand, it points to the fact that the greatest rate-limiting factor to conducting research in the field of donation and transplantation is the continued lack of active research protocols, due in large part to the complexities of navigating the opaque and cumbersome regulatory framework.

In 2013, the Alliance (https://www.organdonationalliance.org) held a consensus conference together with the Health Services Resources Administration (HRSA), the American Society of Transplantation (AST), and the Association of Organ Procurement Organizations (AOPO) to discuss the barriers and the opportunity for the field and to derive a path forward. This work culminated in a 2015 letter from the Alliance to HRSA with a request: "develop an oversight mechanism to enable and facilitate interventional research in deceased donors and donor organs."[5] The idea put forward was to create a centralized oversight committee that would have 3 arms of review: (i) scientific merit of proposed protocols; (ii) ethical oversight, which would include both human subjects research review in an institutional review board (IRB) function as well as deceased donor research review, recognizing that deceased donors are not human subjects and that different ethical principles apply; and (iii) safety and impact monitoring, which is particularly important given that donor management research in the target organ could have clinical impact on "bystander" organs that are not the focus of the research but nonetheless may be subject to an intervention in the deceased donor's body. A centralized mechanism of review would streamline the IRB reviews necessary in

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multi-center trials, consistent with current "single IRB" requirements for federally funded research, and would resolve the issue of not knowing to which transplant program or patient the organ would go when a research intervention is conducted pre-allocation. This request, and the urgent need to address the barriers to conducting donor research, seemed to gain momentum when the National Academy of Sciences (NAS) launched a study in 2016 to "examine the ethical, policy, regulatory, and operational issues relevant to the conduct of research involving deceased organ donors…[and] examine the gaps, barriers, and opportunities for clinical research involving deceased donors that aims to increase the quality and quantity of donated organs available for transplantation, with particular attention to interventions administered to the donor and thus potentially affecting all of the donor's organs."[6]

The NAS ultimately issued a report in 2018 that echoed the request for a centralized mechanism for oversight and review of donor management research but also concluded that the transplant recipients of organs that had been part of donor management research were human subjects participating in the donor management research protocol.[6] The implications of the NAS position added to the regulatory complexity of conducting this research: if a transplant candidate received an offer of an organ that came from a donor that was part of donor management research, the regulatory requirement for human subjects research informed consent would need to be met. However, the allocation process could intercede between the research intervention in the donor and the organ offer to the recipient, undermining the ability to secure a compliant research informed consent in advance from the putative recipient while on the transplant list awaiting an organ offer. In other words, the human subjects for any donor management protocol may not be identifiable until the moment of the organ offer. However, organ offers for specific patient candidates must be accepted or declined in extremely short timeframes (within an hour), creating an untenable context to obtain a research informed consent in compliance with existing regulations.[7] Alternative mechanisms for compliance were noted in the NAS report, such as the possibility for a Secretarial waiver from human subjects research informed consent requirements; however, this would be a matter for the Department of Health and Human Services (HHS) to determine through the Office for Human Research Protections (OHRP), the agency charged with enforcing the applicable regulations. Accordingly, in January 2019, HHS asked the Secretary's Advisory Committee on Human Research Protections (SACHRP) to review the NAS report and to provide recommendations to inform potential future guidance or action by HHS on this topic.

Following discussion at several meetings in 2019, SACHRP approved recommendations to HHS at its July 2020 meeting, which were then communicated to the Secretary of HHS by a letter dated 12 August 2020. In addition to endorsing the benefits of a centralized oversight mechanism, SACHRP recommended that donor management research proceed under a Secretarial waiver, operating under the assumption that it will be rare for donor management research to qualify as "no more than minimal risk" (as to the transplant recipient), a precondition to waiving consent under the available regulatory mechanism.[8] SACHRP recommended that the certain conditions attach to the waiver, including the following: (i) a summary of key information of the research is provided orally to the organ transplant candidate during the organ offer discussion; (ii) the prospective organ transplant recipient receives and signs an IRB-approved information form containing complete research consent information after arrival at the transplant center (but not necessarily prior to surgery); (iii) the single IRB reviewing the research considers additional protections similar to those required for emergency exception from informed consent (i.e., consultation with the community, etc.); and (iv) various educational and informational resources for potential organ transplant candidates and transplant teams are available.[8] SACHRP also noted that a parallel solution under the Food and Drug Administration (FDA) regulatory framework is required—which an HHS Secretarial waiver would not address—and suggested the possibility for FDA rule making with interim enforcement discretion. To date, notwithstanding SACHRP's recommendations, there has been no formal guidance issued by OHRP, Secretarial Waiver implemented by HHS, or FDA-proposed rule making or acknowledgment of enforcement discretion.

The need for resolution of this now decade-long pursuit of a viable pathway to support, conduct, and oversee robust clinical research in the field of organ donation and transplantation is more apparent than ever. The heightened national attention on improving access to transplants has provided a clear focus that the largest opportunity for growth is with organs from older and more medically complex donors—the very pool of potential donors that could benefit most from improved transplant use through

interventions identified by research. A renewed call for a national conversation is warranted. However, that call should first be to finally resolve the long-recognized regulatory barriers that continue to thwart innovation through clinical research in the field.

DISCLOSURE

Both authors declared no competing interests.

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