The Alliance
LEADERSHIP IN ORGAN DONATION AND TRANSPLANTATION

September 2, 2015

Robert Walsh
Director, Division of Transplantation
Health Resources and Services Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Mr. Walsh:

As the donation and transplant community continue their multi-faceted efforts to address the ongoing shortage of transplantable organs, we are writing to request that the Division of Transplantation (DoT) develop an oversight mechanism to enable and facilitate interventional research in deceased donors and donor organs.

I. Executive Summary

Innovative deceased donor interventions offer the potential to address the disparity between organ supply and demand by significantly increasing the quantity and quality of organs available for transplantation. The impact of this could be far reaching, mitigating prolonged waiting times and the associated morbidity and mortality incurred by transplant candidates awaiting a transplant and mitigating reductions in recipient survival attributable to inferior organ quality. The professional donation and transplantation community believes that the relative paucity of research trials in the field of donation and transplantation is due to the multiple logistical, regulatory, and ethical barriers that exist. As a result, very little evidenced-based medical innovation related to deceased donor management and/or therapies or ex vivo organ preservation and/or repair has occurred in the field.

The primary roadblock identified is the inability to navigate how deceased donor research maps to the existing federal regulatory requirements for review and approval of human subject research. The complications fall into three categories: (1) deceased donors are not human subjects and yet some level of ethical review is appropriate and requested by donor hospitals; (2) the processes of organ allocation and distribution after a donor research intervention complicates the ability to obtain prospective Institutional Review Board (IRB) review and approval as well as prospective informed consent from, transplant recipients that qualify as human research subjects; (3) there is no mechanism for safety monitoring of how a donor research invention may impact recipients of the targeted (i.e. studied) and non-targeted organs as well as any impact on organ donation and distribution.

We believe that all three of these barriers would be significantly resolved by the creation of a mechanism for coordinated centralized oversight that could provide a scientific and ethical review of proposed research with regard to the deceased donor and organ recipients, serve as the IRB review for those studies that will enroll human subjects and evaluate the safety aspects of proposed research including potential impact on recipients of the non-targeted organs and broader issues of concern to the donation and transplantation communities. Construction of a mechanism for centralized oversight would greatly facilitate the ability to conduct wide-scale donor research trials while preserving the public and professional trust in the stewardship of organs as a scarce resource through the existing system of donation and transplantation. Because efficiency, subject matter expertise and expedient decision-making are necessary to ensure that the new oversight structure diminishes existing barriers rather than create new ones, we propose that the centralized review mechanism be constructed outside of the existing OPTN framework and maintained through contract with an entity that brings expertise and experience in clinical research trials and deceased donation. We believe that the time is now and urge HRSA to act on this proposal.

II. Background

Over the last four years, a consortium of transplant organizations (including professional societies, members of the organ procurement community, and governmental agencies) have held a series of meetings to define and discuss the obstacles to conducting deceased donor research. The genesis of this effort was spearheaded by the American Society of Transplant Surgeons dating back to 2010, with the Organ Donation and Transplantation Alliance (The Alliance) leading the effort since 2013. Some of the foundational questions this group has spent time discussing and analyzing include: How is authorization for research in deceased donors obtained and when is it required? How are the candidates on the waiting list and their physicians informed about the research intervention? When is the recipient of an organ that was part of a research intervention considered a human subject?

Most recently, with support of The Alliance, the consortium began to draft an architectural framework that could facilitate donor intervention research. The principal component consists of a centralized oversight mechanism that would address all of the existing barriers through one mechanism. The perceived value in constructing a national framework for deceased donor research is efficiency to facilitate the conduct of this vital research, coupled with transparency and consistency with principles of research ethics that are vital to preserving the public and professional trust in this important work.

The organizational and individual stakeholders that donor intervention research trials might encompass is vast, inclusive of not only deceased donors and their families, but also organ procurement organizations (OPOs), donor hospitals, transplant candidates and recipients, transplant physicians and centers, researchers, IRBs, OPTN/UNOS, SRTR and multiple governmental agencies including the FDA, HRSA, NIH, CMS and OHRP as well as accrediting agencies such as The Joint Commission and Association of Organ Procurement Organizations (AOPO). The number and diversity of these constituencies articulates the need for HRSA to spearhead efforts to facilitate the development of a national framework that will allow the ethical and safe conduct of rigorous donor intervention research trials that may lead to game-changing

innovation in deceased donation and transplantation. It is the consortium's opinion that the complexity of the issues and numerous barriers are of a magnitude that requires federal action.

III. The Proposal

The centerpiece and singular most important request in this letter is the development of a central oversight committee (COC) that will be charged with the review, supervision, and monitoring of all donor intervention trials conducted within the U.S. The COC role would require a broad range of expertise to properly function in three areas: the scientific merit of any proposed intervention, the ethical conduct of research in both deceased organ donors and organ recipients (whether or not they are human research subjects as currently defined in federal regulation), and the impact of research on transplant recipients of targeted and non-targeted organs, candidates on the waiting list, and the donation and transplant communities.

A. Centralized Oversight

One of the primary barriers identified is the current perception that IRB review and approval is required at each institution that may be implicated by any human subjects research component of deceased donor research. This assumption can result in deceased donor researchers seeking prospective IRB review and approval at any transplant program that might receive an offer of an organ under the study protocol. This is simply untenable and has been cited in the literature as a primary reason these types of trials are not conducted. A centralized review process would eliminate this barrier by designating the COC as the IRB of record for all other institutions participating in the research.

Central oversight is also important as organ distribution is progressively becoming more geographically diverse. As a consequence, trials conducted in either deceased donors or in procured organs have the potential to impact transplant patients, physicians, and centers nationally. We envision that collaboration to share data and analytic expertise among the COC and the OPTN as well as the SRTR will be essential to enable assessment of potential impact on organ allocation and distribution, on waiting list morbidity and/or mortality, and on the outcomes of transplantation for the non-targeted organs. There is a precedent for centralized review and oversight in the healthcare community on a national basis; the National Cancer Institute Central Institutional Review Board Initiative (https://ncicirb.org/cirb/default.action) is one example. Furthermore, there is currently a national shift towards centralized review of human subjects research. The NIH has recently begun to require centralized review as a condition of certain grants and issued a draft policy to promote the use of single IRBs for all NIH-funded multi-site research. Furthermore, the anticipated revisions to the federal human subjects research regulations are expected to contain a centralized review requirement. As such this request aligns with efforts in other areas of biomedical research.

As currently envisioned, the COC would be best maintained under contract with a non-governmental third party (similar to the OPTN or the SRTR). The primary reason for this recommendation is the need for the COC to possess full-time dedicated staff with significant subject matter expertise (in human subject research regulations for example) and the ability to make well-informed expedient decisions on pending (often complex) research proposals. The importance of timeliness and responsiveness as a core requirement is vital to ensure the new oversight structure diminishes existing barriers rather than creates new ones. Further, the ability

to adapt to evolving trends in donor intervention research over time is a key component to this structure being successful in facilitating innovation through research in our field. All of these critical features point to a contractual relationship with an independent entity capable of delivering substantive expertise in a nimble manner. This is not a function that can be carried out by volunteer committee members that meet infrequently.

B. Committee Structure

The COC would have three broad functions with responsibility assigned to different work groups; scientific merit review, ethical oversight, and safety and impact monitoring (See attached diagram). Coordinating these separate functions within a single committee organization to oversee these complex trials will offer several benefits including an adept review and oversight process and a level of expertise that would be difficult to replicate at a local or regional level. The following provides detail of each of the three core functions.

Scientific Merit: The nature of donor intervention research requires that there is a rigorous process of scientific review to assess the adequacy of preclinical studies, the study design, the plan for data analysis, and the overall merit of the proposal. Expert independent reviewers would be asked to evaluate the proposed studies and assess the merit of the intervention as compared to the potential risk to transplant recipients that the proposed research presents.

Ethical Oversight: Donor intervention trials have the potential to raise distinct ethical concerns that are not adequately addressed under existing ethical frameworks for human subjects research. This is primarily due to the fact that the ethical principles relevant to decedents are not based around risks of harm and potential benefits. The ethical oversight workgroup would assess and review proposed research interventions in the deceased donor consistent with a developed ethical framework appropriate for consideration of research in deceased donors. The workgroup would also determine whether the involvement of recipients of targeted organs qualifies as research in human subjects and provide appropriate review and oversight accordingly. This means the workgroup, given an appropriate composition, would qualify as an IRB and act in that capacity under the existing regulatory requirements as necessary.

Safety and Impact Monitoring: Once studies are initiated, the impact of research interventions conducted in deceased donors has the potential to alter organ allocation and distribution for both the targeted and the non-targeted organs. This should be assessed in real time, to the greatest degree possible. With respect to the safety of recipients of targeted organs, study-specific Data Safety Monitoring Boards (DSMBs) would have the primary burden. These study-specific DSMBs would report to the COC such that the latter has access to timely information regarding the safety profile of ongoing trials. Beyond the recipients of targeted organs, the safety and impact on the recipients of non-targeted organs must also be assessed. The primary responsibility for this would reside within this workgroup of the COC.

C. COC Jurisdiction

The effectiveness of this framework is dependent on a requirement that all clinical trials involving interventions to deceased donors or to deceased donor organs come under the COC. The authority of the COC to act as the IRB of record for other institutions to the extent that human subjects research is being conducted as part of the research is also critical to remove one of the significant barriers that exist today. These goals could both be accomplished through OPTN/UNOS policy requirements.

On the donor side, it will be important that the COC serve as a recognized authority on ethical review and oversight of research on deceased donors. Requiring ethical review and approval of the donor research that can be confirmed would provide confidence to donor hospitals that appropriate oversight exists. A regulatory directive for donor hospitals to accept this review in lieu of local institutional review could come from CMS, assisted by a clarification from OHRP that donor research does not require IRB review. This would directly address one of the significant existing barriers - the donor hospital's misperception that research on deceased donors must be reviewed by an IRB.

IV. Conclusion**:**

The absence of recognized ethical guidelines and a regulatory infrastructure for innovative research in deceased donors prevents the translation of laboratory-proven strategies to protect and optimize organs for the benefit of patients. Even if trials were to take place, the current lack of centralized oversight risks the erosion of public and professional trust in stewardship of organs as a scarce national resource. The consortium believes that HRSA, and specifically DoT, should lead the creation of centralized oversight mechanism as outlined in this letter to facilitate innovative and rigorous deceased donor intervention research. Well-designed and well-executed donor intervention trials offer tremendous potential to increase both the quantity and quality of organs for transplantation, thereby saving lives and improving the health of patients.

We are aware of and have been participating in efforts with the Institute of Medicine as they consider a study on this exact topic. Nonetheless, we urge HRSA and the DoT not to await the results of that effort to take action. It will take time to build the framework proposed and that foundational work must be completed before significant trials can be underway. With 22 people dying on the waitlist every day, the need to enable and facilitate innovative deceased donor research is clear and should not be further delayed.

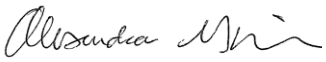
We look forward to working with you and other members of HRSA and the DoT on this initiative.

Sincerely,

Peter Abt, MD
DIREP Committee Co-Chair

Rick Hasz
DIREP Committee Co-Chair

David Nelson, MD
DIREP Committee Co-Chair



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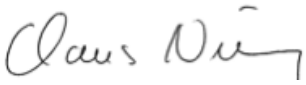

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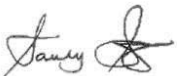

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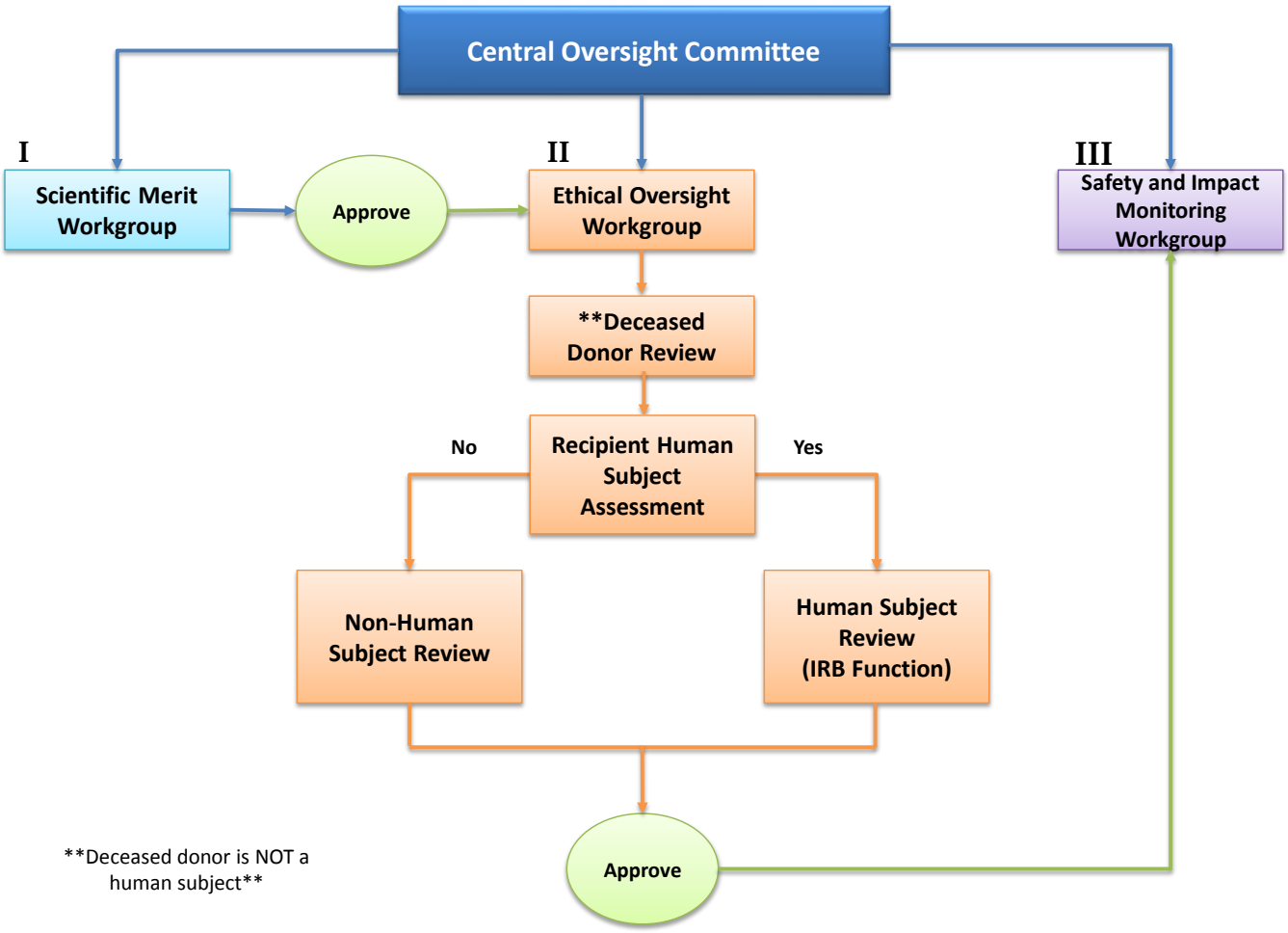
Attachment I

The Central Oversight Committee



Attachment II
Members of the Donor Intervention Research Expert Panel

Contact	Title	Organization
Kim Gifford	Executive Director	American Society of Transplant Surgeons
Elling Eidbo	Executive Director	Association of Organ Procurement Organizations (AOPO)
Libby McDannell	Executive Director	American Society of Transplantation
James Rodrigue, PhD	Transplant Psychologist	Beth Israel Deaconnes Medical Center
Susan Stuart	President, CEO	Center for Organ Recovery & Education
Mary Rydman	Director HRPO	Dignity Health
Claus Niemann, MD	Professor of Anesthesia & Surgery	University of California, San Francisco
Rick Hasz	Vice-President, Clinical Services	Gift of Life Donor Program (PA)
Richard Pietroski	CEO	Gift of Life Michigan
Peter Abt, MD	Transplant Surgeon	Hospital of the University of Pennsylvania
Kim Olthoff, MD	Chief, Division of Transplant Surgery	Hospital of the University of Pennsylvania
Tim Taber, MD	Medical Liaison	Indiana University Transplant Institute
David Nelson, MD	Chief of Heart Transplant Medicine	Integris Baptist Medical Center
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Kevin Myer	President/CEO	LifeGift
Jeff Orlowski	Chief Executive Officer	LifeShare Transplant Donor Services of Oklahoma
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LeAnn Swanson	Executive Director	Organ Donation and Transplantation Alliance
Darren Malinoski, MD	Chief, Section of Surgical Critical Care	Portland VA Medical Center
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Roslyn Mannon, MD	Professor of Medicine	University of Alabama at Birmingham
Tracy Koogler, MD	Associate Professor of Pediatrics	University of Chicago
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