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Regulatory Innovation: Not an Oxy-Moron

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CEOT CUTTING EDGE of TRANSPLANTATION

TRANSPLANT SUMMIT 2018

Breaking Through Regulatory Barriers to Unleash Transplant Innovation

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Disclosures

- CEO of New England Donor Services, running 2 OPOs (New England Organ Bank and LifeChoice Donor Services) – compensated to further the mission of saving lives through donation and transplantation.

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Minireview

Donor Intervention and Organ Preservation: Where Is the Science and What Are the Obstacles?

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The organ shortage is widely acknowledged as the most critical factor hindering the full realization of success for solid organ transplantation. Innovation in the areas of donor management and organ preservation offers the most realistic hope to improve both the quality and size of the current organ supply. Although the basic science dissecting the complex processes of brain death and ischemia/reperfusion injury is replete with exciting discoveries, the clinical science investigating donor management and organ preservation is sparse in contrast. This review will survey the current landscape of trials to mitigate organ injury through interventions administered to donors *in vivo* or organs *ex vivo*. Consideration will then be given to the scientific, logistical and ethical obstacles that impede the transformation of laboratory breakthroughs into innovative treatments that simultaneously improve organ quality and supply.

Which of statement is true?

A) deceased donors are human subjects under the fed regs and IRB approval is required

B) deceased donors are not human subjects under the fed regs but IRB approval is required

C) deceased donors are not human subjects under the fed regs and IRB approval is not necessary but there are other laws that apply

D) deceased donors are not human subjects under the fed regs and IRB approval is not required. There is no direct regulation of research on deceased donors.

D)

Regulatory Ambiguity

Deceased Donor Intervention Research: A Survey of Transplant Surgeons, Organ Procurement Professionals, and Institutional Review Board Members

J. R. Rodrigue[1,2,*], S. Feng[3], A. C. Johansson[2,4] A. K. Glazier[5] and P. L. Abt[6]

American Journal of Transplantation

Survey of OPO directors, Transplant Surgeons, IRB members

- Variety of research scenarios
- Disagreement with regard to recipient consent and the necessity of IRB approval

Progression of national work to address barriers

- 2013 the Alliance convened a consensus conference
  - 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?
- DIREP Committee developed a proposed solution
- Letter to HRSA in 2015

The Alliance
LEADERSHIP IN ORGAN DONATION AND TRANSPLANTATION

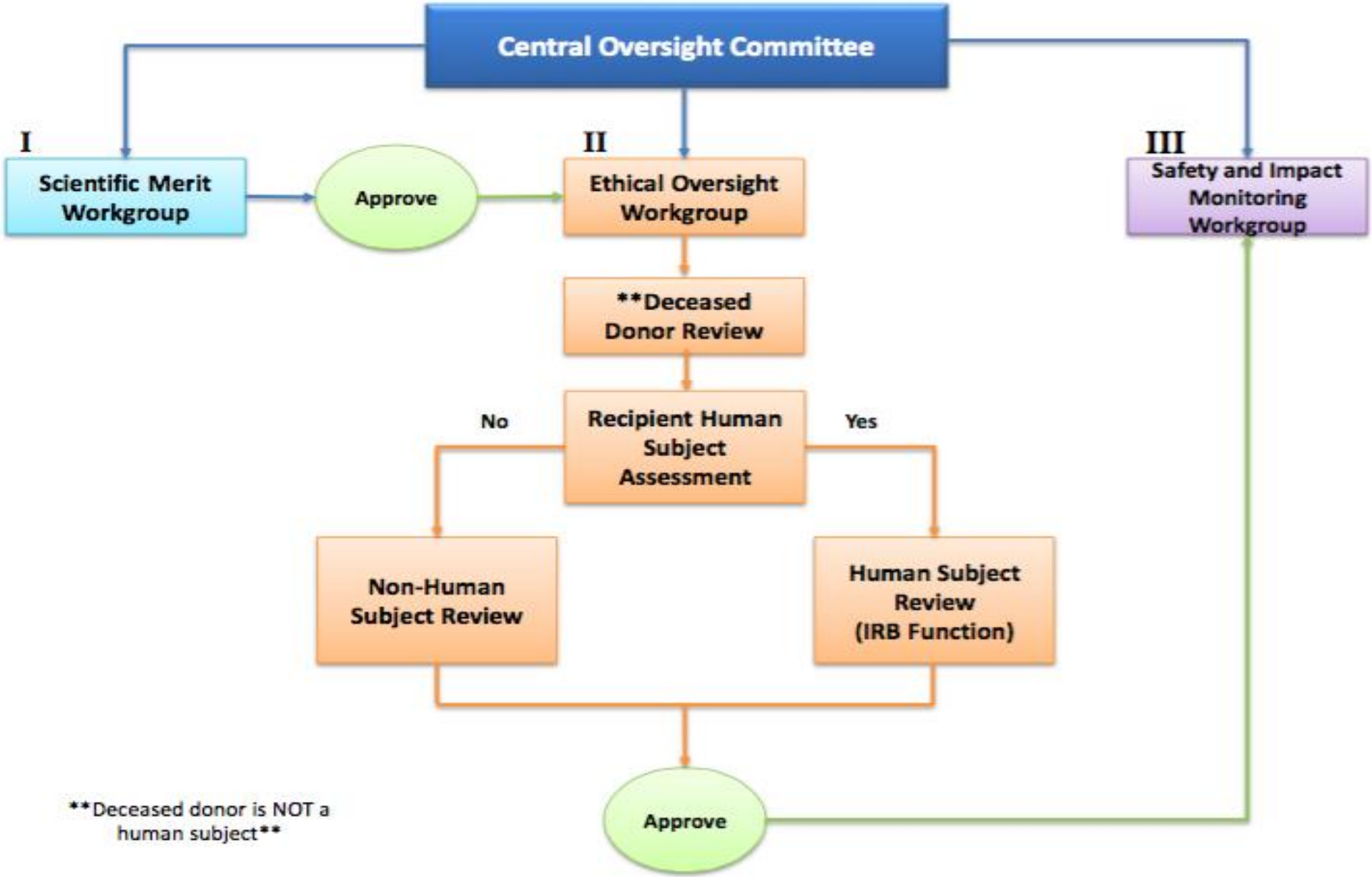
September 2, 2015

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


Central Oversight Committee
I
Scientific Merit Workgroup
Approve
II
Ethical Oversight Workgroup
III
Safety and Impact Monitoring Workgroup
**Deceased Donor Review
Recipient Human Subject Assessment
No
Yes
Non-Human Subject Review
Human Subject Review (IRB Function)
Approve
Deceased donor is NOT a human subject

Why the National Academy of Science?

- Provide an independent level of scholarly review
- Negates conflict of interest
- Well respected by medical community and the public
- NAS has a history of providing guidance and clarity to the development of organ donation and transplantation

NAS: Statement of Task

An ad hoc study will examine the ethical, policy, regulatory, and operational issues relevant to the conduct of research involving deceased organ donors (for purposes of the study, the concept excludes interventional research preceding declaration of death by neurologic or cardiopulmonary criteria among potential organ donors). The committee will 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.

What are the biggest barriers to conducting multi-center clinical trials in donation and transplantation?

a) Donor authorization for research?
b) Donor registry systems?
c) Multiple IRB approvals?
d) Consenting recipients of organs that were subject to a research intervention?
e) Allocation challenges?

NAS Study October 2017: Goals and Recommendations

- Goals 1, 2 and 3: Donor
  - Increased transparency through donor registration process and legal clarification of donor authorization
- Goal 4: Recipient
  - Informed consent within complexities of system
- Goal 5 and 6: Oversight
  - Centralized review mechanism to facilitate transparency, equitable and high quality research

Defining Research in the Deceased Donor Context

- "research" is a systematic investigation designed to contribute to generalizable knowledge.

- Research purpose may exist even if transplantation is also planned

- Dual purpose of transplant and research

Deceased Donor Authorization

- Legal Framework
  - Uniform Anatomical Gift Act (UAGA)
    - Donor or Surrogate can provide legal authorization
    - Based on gift law not informed consent principles
  - Permission for the “what”
    - Organs
    - Tissues
  - Permission for the “why”
    - Transplantation
    - Research
    - Education

Deceased Donor Authorization for Research followed by Transplant

- Multiple pathways to obtain permission
  - Donor authorization
    - Donor Registry
    - Document of gift
  - Surrogate authorization
    - Family permission at time of donation

- Information for donor families and donor hospitals
  - Transparency / use of gift

What does donor authorization for research followed by transplant look like?

- *Donated organs may be transplanted as part of clinical research. An example of this type of research is studying whether placing donated organs on a device before transplantation improves results for transplant recipients.*

- *The management of the donor prior to the surgical recovery of donated organs may include research measures designed to study ways of improving organs for transplantation. An example of this type of research is studying whether giving a drug after the donor has died but prior to organ donation improves results for transplant recipients.*

Innovating Regulatory Assumptions: When Recipient is a Human Subject?

- A) A recipient of an organ that has been subject to a research protocol is a human subject because the transplant is experimental
- B) A recipient of an organ that has been subject to a research protocol is not a human subject unless there are other protocol interventions on the recipient
- C) A recipient of an organ that has been subject to a research protocol is a human subject because the organ is experimental
- D) It depends

Innovating Regulatory Assumptions: When Recipient is a Human Subject?

- There is *research*:
  - Intent to collect information about the recipient in a controlled manner in order to contribute to generalizable knowledge
- There is a *human subject*:
  - Research driven interventions (i.e. blood draws, biopsies) performed in connection with transplant
  - Research driven data collection beyond de-identified or coded standard of care outcomes and clinical data
  - Identifiable private information

Innovating Regulatory Assumptions: When Recipient is a Human Subject?

- Receiving a "research organ" alone may not make the transplant recipient a human subject
  - No intervention/interaction for research purpose; clinically motivated
  - Organ is not an "investigational agent"
- Prior research on the donor or organ does not necessarily result in an "experimental" transplant
- Prior research on the donor or organ may be a donor factor comparable to other organ specific donor risk factors
  - Recipient needs to be informed as part of clinical consent for transplant
  - Does not necessarily convert the transplant recipient into a research subject

Innovating Regulatory Assumptions: When Recipient is a Human Subject?

- Clinical informed consent should address any risks from organ research
- If organ recipients qualify as human subjects, the “risk” of such research may often be no more than minimal
- Alteration of consent requirements by IRB may be an option to consider under existing regulatory criteria
- Secretarial waiver

Proposed Conclusion

- Not all recipients of organs involved in donor research protocols are research subjects

- Receiving “research organs” alone does not technically make the recipient a “human subject”
  - NAS assumes recipient will be human subject in most instances
  - OHRP yet to clarify
  - Centralized Review Board may take this up

- The degree of oversight and consent applied to recipient research should be keyed to the degree of risk involved

- Recipients of bystander organs require clinical safety monitoring and consideration of risks to non-subject third parties

Centralized Review of Research

- Donor-Research Oversight Committee (DROC)
- Single review and approval opportunity
- Centralized information about ongoing trials
- Coordinate safety monitoring

NEXT STEPS

- Focus on the NAS recommendations with the biggest return on investment in the field
- Work to establish centralized oversight mechanism
- Set public expectation normalizing research followed by transplantation
- Expand opportunity for clinical innovation

What is the primary goal of regulating clinical trials in donation and transplantation?

a) Stewardship of donated organs
b) Public and professional trust through transparency
c) Oversight and facilitation of innovation


PHARMACOLOGICAL
DRUG TRIAL RESULTS
OUR TRIALS SHOW THAT
THE NEW DRUG PERFORMS
NO BETTER THAN PLACEBO
MAYBE WE SHOULD
INVEST IN PLACEBOS
CHRIS
MADDEN