Approaches to Organ Donor Intervention Research Study Design

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Disclaimer

- The views expressed today are my own and do not represent those of the Brigham and Women’s Hospital or the President or Fellows of Harvard University.

- I am the immediate past chair of the Secretary’s Advisory Committee on Human Research Protections, a committee that did not consider this issue during my tenure.

- I am on the Board of Directors of PRIM&R, MSH, CliniThink, the Edward P Evans Foundation, and the Scientific Advisory Board of Molecular Stethoscope. I am or have been an expert witness for a hospital, Abbvie, Lilly, and a university.

- None of these relationships are relevant to this presentation.
The initial question: is this research?
- It depends

Walking the line between societal and ethical standards and the regulations

A few approaches and suggestions
Is this research?

- The Paradigm:
  - Organ
    - Standard of care
    - “Back table” organ
    - Deceased donor in which donor organ has been “manipulated”
    - Innocent “bystander” organ, organs other than the organ of interest that nevertheless are affected by treatment of deceased donor
  
  - Recipient
    - From which no additional information will be obtained for research purposes
    - On or from which research procedures or information (data) will be obtained.
Human Subject:

- A living individual about whom an investigator conducting research obtains:
  - Data through intervention or interaction with the individual; or
  - Identifiable private information.

Thus, the organ is *never* a human subject. The organ and/or the deceased is always deceased.

The specific case of research on the donor organs of living related or unrelated donor → Research
And although not “research:”

- The Organ Donor Family:
  - Not research, by regulatory definition of research
  - Nevertheless, my understanding is that it is common practice to ask permission of the donor family to subject the organ (or deceased) to experimental procedure, regardless of the change from standard of care. “Research Authorization” (under gift law.)
  - And possible to embed in this authorization permission for “extra bits”
  - Customary practice
  - Respectful of the family and promotes public trust
  - Appears to conform to societal expectations--countervailing arguments exist
  - Limits organ availability
  - Public education essential
Is it research: The recipient?

Research:

- A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

- The recipient

  - Standard of Care (SOC)
  - Collect only deidentified clinical information → Not research or, if highly technical, minimal risk research
  - Collect identifiable information for research purposes → Research
  - Perform research procedures → Research (minimal risk or not, depending on procedure)
For purposes of discussion:

- Standard of care
- (Notably, SOC is not uniform)

- Minimal risk research
- (e.g. oT, pulse of methylprednisolone, washout, etc.)

- Treatment with new investigational product
- Gene therapy

QI vs Research?
The recipient

- The recipient
  - It depends
  - SOC

- Collect retrospective data Hospital A vs. B → Not research
- Randomize treatments to Rx A vs. Rx B → Research
- CRT: Hospital A vs. Hospital B → Research

- But if randomized treatments, offered with knowledge of specific treatments to transplant physician, then individual physician choice → Not research but clinical care.
- Clinical consent, not research consent
The recipient

- The recipient
  - It depends
  - Minimal Risk

- Randomize treatments to Rx A vs. SOC or vs. Rx B → Research
- Treat organ with Rx A with knowledge of specific treatments to transplant physician → is this clinical care (and therefore appropriate for clinical consent) or research? But if require research consents, will slow progress of science.

- Regulatory: (I think) research (although reasonable people might disagree and have disagreed): “indirect” manipulation
- Ethical: Given state of current knowledge, argument that notice would be sufficient, with opportunity to opt out.
The recipient

• The recipient
 ➢ Research
  ➢ Treatment with new investigational product
  ➢ Gene therapy

➢ Any study design, information collection → Research
➢ Treat organ with Rx A with knowledge of specific treatments to transplant physician → gut check: Research

➢ But what does that mean for the participant?
➢ And what practical and logistical implications are entailed?

➢ Applicable to all transplant research
The recipient and transplant centers

• The recipient
  - The individual potential recipient is only notified at the time of (likely) availability of donor organ.
  - The potential recipient is often acutely ill (or on chronic, life-limiting therapies [e.g. dialysis] and cannot be secured of timing of alternatives.
  - The immediate situation is urgent/emergent
  - Potential for ‘undue influence’
  - Delay in decision compromises organ viability while the clock is ticking.

• The transplant setting
  - Local IRB review at full board is not possible at the time, may require emergency approval (never ideal), and introduces problematic delays in allocation and other issues
  - Inappropriate to consent all potential recipients to all potential studies
The recipient: potential approaches

**The recipient**
- Ask all potential recipients whether or not they wish to be considered for a “research organ,” at a quiet time outside of the transplant offer
  - Allows adequate time for education, questions and discussion
  - Would require the maintenance of two (SOC, research) or three (SOC, minimal risk research, high risk research) lists by agency.
  - Still permits opt in/opt out at time of transplant when specifics – both of the research and of the current clinical situation – are known.
  - Arguably respectful of autonomy interests
- Other models possible (global consent, etc.), many problematic

**IRB review**
- Likely requires utilization of central IRB (e.g. single site review for multisite research)
National IRB network

National Network with
- One Authorization Agreement
- Common workflow
National IRB network

As of 12/12/2016

70 Participating Institutions
42 CTSA hubs

SMART IRB

Supporting single IRB review.
Advancing collaborative research.

Advancing research together.
SMART IRB is a platform designed to ease common challenges and burdens associated with initiating

Will change the ability to review and approve research:

- Single review
- Single informed consent with locked and open (e.g. whom to contact) domains
Potential approaches

• The most problematic
  - Temptation to define as QI
  - Minimal Risk

  ➢ Assume that we wish to advance the science
  ➢ Given regulatory constraints, and the fact that waiver of informed consent is not possible under the current regulations (consent is always “practicable,”) so how to approach?

  ➢ OHRP to communicate intention to apply enforcement discretion
  ➢ Or, Secretarial Waiver in settings of minimal risk research (or minor increase over minimal risk research), with notice and comment, and requirement that:
    ▪ Adequate information be given in the clinical consent regarding prior research on organ, research (and clinical) information as known
    ▪ Ability of recipient to opt in/opt out of clinical/research transplant

  ➢ Public education and engagement essential
§ 46.101 To what does this policy apply?

(i) Unless otherwise required by law, department or agency heads may waive the applicability of some or all of the provisions of this policy to specific research activities or classes or research activities otherwise covered by this policy. Except when otherwise required by statute or Executive Order, the department or agency head shall forward advance notices of these actions to the Office for Human Research Protections, Department of Health and Human Services (HHS), or any successor office, and shall also publish them in the FEDERAL REGISTER or in such other manner as provided in department or agency procedures.

Need to identify risks of research

- OPTN, OPOs with, if advisable, national multi-disciplinary advisory bodies to
  - Review planned programs for organ “manipulation” and research
  - Review scientific merit and assign risk of procedure or process to organ
  - Align endpoint selection
  - Specify additional ethical concerns and mitigation strategies
  - Assign safety monitoring requirements
  - Periodically review and assess protocols, robustness and comparisons of endpoints, safety endpoints, etc. and create learning environment

- Communicate publically and transparently
- Revise process as required
A word about “bystander” organs

Back table treatment of organ → no impact on bystander organs

Deceased donor treatment → assess likelihood of bystander impact, arguably different on different organs

Same paradigm As presented
Summary

- Study elements: agreement on (surrogate) endpoints, tolerance of randomized design
- Appreciation of risk of ‘marginal’ or ‘expanded criteria’ and willinness to disclose
- Commitment to, and advice on, transparent and informed clinical consents
- Dependence on national IRB reliance network
- Risk-based approach to research
- Use of enforcement discretion and/or Secretarial Waiver at § 46.101(i)
- Potential for election to cohort assignment to respect risk-tolerance outside of acute clinical setting
- Coordination and recommendations of OPOs, OPTN, and national multi-disciplinary advisory bodies
- Public education and community engagement
Questions, Discussion
And Thank You

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Waiver of IC

§ 46.116 General requirements for informed consent.

• (d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:
  • 1) The research involves no more than minimal risk to the subjects;
  • (2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;
  • (3) The research could not practicably be carried out without the waiver or alteration; and
  • (4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.