PUBLICCITIZEN
1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

Promoting Public Trust in Organ Donor Intervention Research

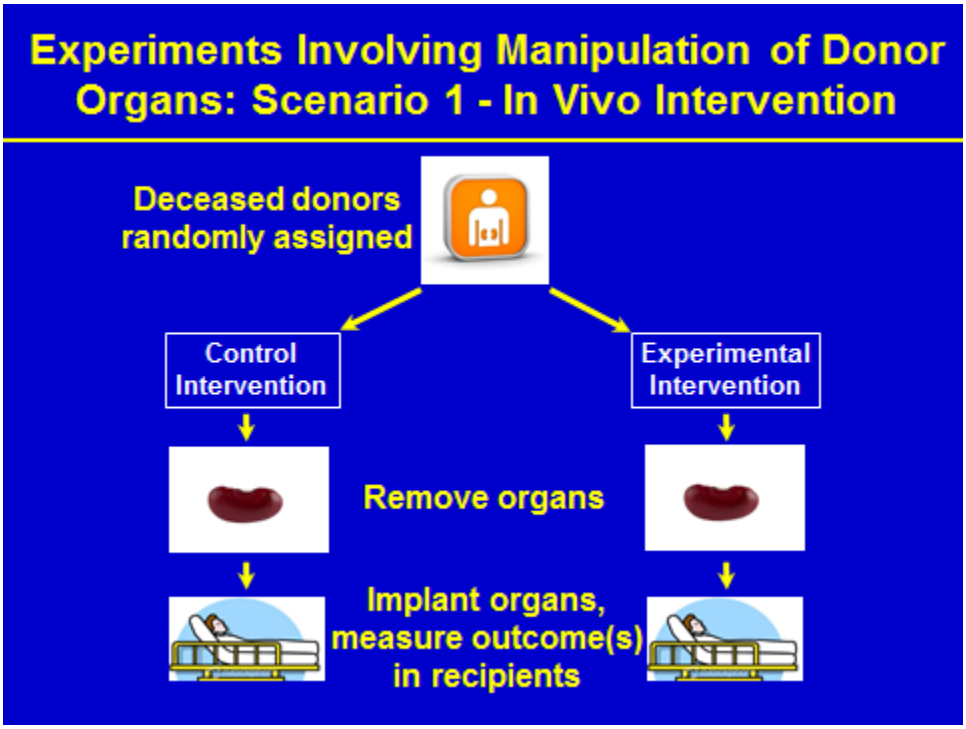
Presentation by Michael Carome, M.D. at the December 14, 2016, Meeting of the Committee on Issues in Organ Donor Intervention Research, National Academies of Sciences • Engineering • Medicine

Good Afternoon. Thank you for the opportunity to address the Committee. I was asked by Committee staff to describe the policy positions that Public Citizen would like to see the Committee take regarding organ donor intervention research.

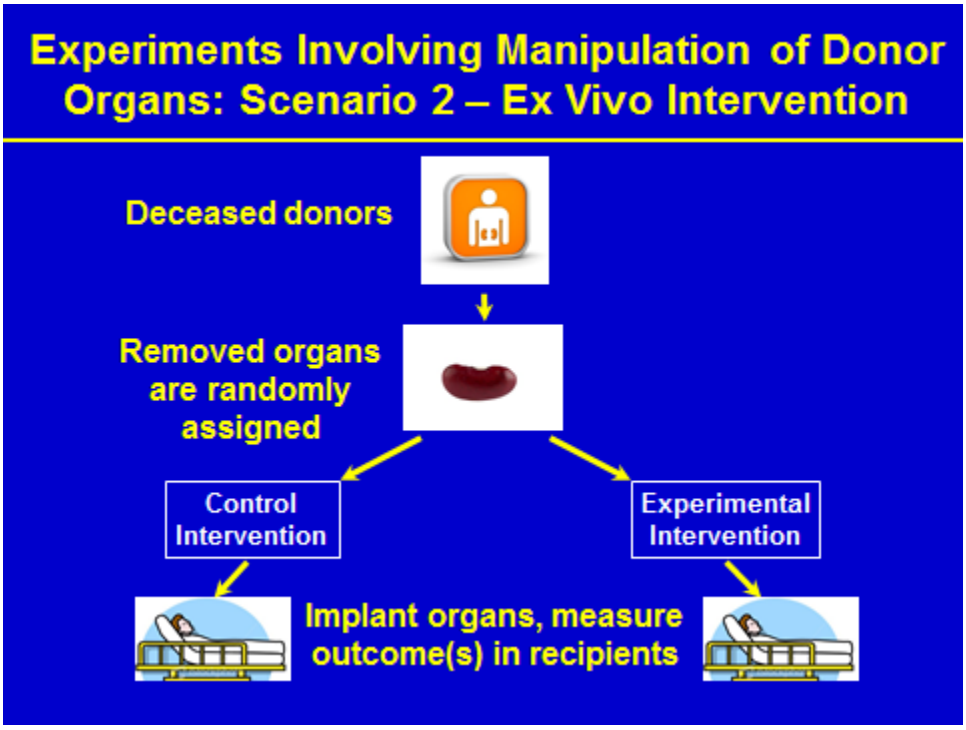
Promoting public trust in organ donor intervention research requires, among other things, the following three key actions:

- Recognize and acknowledge that such research is non-exempt human subjects research under applicable federal regulations
- Obtain the voluntary informed consent of the transplant organ recipients, who are the human subjects of the research
- Ensure appropriate and meaningful institutional review board (IRB) review of the research

There are two basic scenarios for experiments involving manipulation of donor organs prior to transplantation. The first involves an intervention delivered to the deceased donor prior to organ removal. The committee's charge relates to this scenario.



The second scenario involves an intervention involving donor organs after they have been removed from the donor.



My comments will focus on the living patients in whom the experimentally manipulated donor organs are transplanted and clinical outcomes are measured. Addressing the ethical considerations regarding the deceased organ donors and the recipients of other organs that are not being studied is also important to promote public trust in such research, but I will let other members of this panel speak to those issues.

In both scenarios, the investigators are not evaluating the experimentally manipulated donor organs in isolation in a laboratory. Rather, the experimental manipulations of donor organs are targeted primarily at the transplant organ recipients: The investigators want to test whether the experimental manipulations of the donor organs affect clinically important outcomes in the transplant recipients, such as short- and long-term renal function and need for dialysis in kidney transplants, glucose control in pancreas transplants, and patient survival in liver, heart, and lung transplants.

The Committee is very familiar with the definition of *human subject* under federal regulations for the protection of human subjects (the Common Rule; see for example, 45 C.F.R. § 46.102(f)):

> *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains
>
> (1) Data through intervention or interaction with the individual, or
>
> (2) Identifiable private information.

> *Intervention* includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

That experiments involving manipulation of donor organs prior to transplantation into the recipients are human subjects research is not even a close call. These experiments involve both interventions — the implantation of experimentally manipulated donor organs — and the obtaining of identifiable private information — including clinical outcomes in the transplant organ recipients. The investigators conducting these experiments seek to evaluate the potential benefits and risks of experimental interventions directed at the donor organs for the recipients of those organs.

It was reassuring to see that the Department of Veterans Affairs' Office of Research Oversight (ORO) promptly reached this same conclusion regarding hypothermia kidney transplant clinical trial published by Neimann et al in 2015[1] following the agency's investigation of Public Citizen's complaint about the trial.[2] ORO's October 2016 letter to Public Citizen — a copy of which has been provided to the Committee — clearly articulated in detail why this trial involved human subjects research. This type of agency action promotes public trust in such trials.

At the same time, ORO's statement in its letter that "given the widespread uncertainty within the transplant community, ORO acknowledges that other federal agencies may well come to different conclusions regarding application of the Common Rule to their deceased organ donor intervention research" fosters doubt and undermines public trust in such research. So too does the OHRP's refusal to open a formal investigation into Public Citizen's complaint and its failure to take a leadership role by joining with ORO in declaring what should be obvious to OHRP staff: that the hypothermia kidney transplant trial was human subjects research.

[1] 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.
[2] Department of Veterans Affairs, Office of Research Oversight. Letter to Public Citizen. October 26, 2016. http://www.citizen.org/documents/2315_VA-ORO-Final-Response-Letter_October%2026,2016.pdf. Accessed December 7, 2016.

ORO also noted that "In the course of its review, ORO identified considerable uncertainty and confusion within the transplant community regarding the application of federal human research protection requirements to deceased organ donor intervention research…"

ORO cited results of a recent survey study of IRB members, transplant surgeons, and organ procurement organization professionals as evidence for this uncertainty and confusion.[3]

However, the study referenced by ORO revealed that when it comes to recognizing organ donor intervention research as human subjects research, there is little confusion among IRB members and transplant surgeons regarding whether such research involves human subjects or required IRB review.

The study involved, in part, an online survey of IRB members (n=317) and transplant surgeons (n=294) at 100 U.S. solid organ transplant centers. Survey respondents were presented with a few organ donor intervention research scenarios and asked, among other things, whether the hypothetical research involved human subjects and required IRB review.

One scenario was a randomized, controlled trial in which deceased organ donors would be randomly assigned to receive a new agent that affects the immune system and had been shown to improve liver function and survival in animal studies but also to have some liver toxicity. Investigators would assess whether the donor livers were transplanted and collect clinical data on liver function from liver transplant recipients. Key survey results included:

- 94% of IRB members and 93% of transplant surgeons considered the study to be human subjects research.
- 97% of IRB members and 93% of transplant surgeons said the study required IRB review.
- 99% of IRB members and 96% of transplant surgeons said transplant patients who are offered a liver from a study donor should be informed of the study. Of these, 90% of IRB members and 82% of transplant surgeons said the patients' written informed consent should be obtained prior to transplantation.

So what policy positions should the committee take?

The Committee first should declare emphatically that organ donor intervention research like the donor hypothermia kidney transplant clinical trial published by Neimann et al represents human subjects research under federal regulations.

The Committee then should recommend that OHRP and all other federal agencies responsible for the funding, conduct, or oversight of such research issue unequivocal statements to the same effect to the IRB, research, and organ transplant communities.

[3] Rodrigue JR, Feng S, Johansson AC, et al. Deceased donor intervention research: A survey of transplant surgeons, organ procurement organization professionals, and institutional review board members. *Am J Transplant*. 2016;16(1):278-286.

The second key to promoting public trust in organ donor intervention research is to obtain the informed consent (or the permission from the parents or legally authorized representatives) of the transplant recipient subjects. The subjects have a right to be informed about the research. The ethical and regulatory requirements to obtain informed consent of the subjects logically follow the recognition of this research as being human subjects research.

Therefore, the Committee should conclude that — consistent with the Common Rule and the Belmont Report's principle of respect for persons — investigators conducting organ donor intervention research must obtain the informed consent of the transplant recipient subjects prior to the subjects' involvement in the research. The Committee should develop recommendations for enhancing the consent process for the subjects of such research.

The Committee's conclusions and recommendations regarding informed consent should address the following issues:

- Waiver of informed consent: In most, if not all, cases, such research will not be eligible for waiver of informed consent under the Common Rule (particularly, given the required IRB finding that the research could not practicably be carried out without the waiver). It should be very practicable to carry out this research with the informed consent of the transplant recipients. When consent is being obtained for the transplant itself, consent for the research can also be obtained.
- Timing of obtaining informed consent: This could occur at one or more of the following times: at time of placement on the transplant waiting list, while on the waiting list, or between notification of an organ becoming available and the transplant surgery. When candidates for kidney transplantation are placed on the waiting list, they are asked whether they are willing to receive certain types of kidneys, such as expanded criteria donor kidneys (donors age 60 or older; or donors age 50-59 with two of following: stroke as cause of death, history of hypertension, serum creatinine greater than 1.5 mg/dl[4]). Patients could similarly consent or refuse to consent to receiving kidney from a donor intervention clinical trial.
- Minimizing the possibility of coercion or undue influence when investigators obtain consent: It is probably not possible to eliminate the possibility of undue influence for such studies, and for liver, heart, and lung transplants, there likely will be substantial undue influence.
- Disclosure to the subjects that the research may involve risks to the subjects that are currently unforeseeable.

The third key to promoting public trust in organ donor intervention research is to ensure appropriate and meaningful IRB review of the research.

[4] United Network for Organ Sharing. *Talking About Transplantation: What Every Patient Needs to Know*. 2013. https://www.unos.org/wp-content/uploads/unos/WEPNTK.pdf. Accessed December 12, 2016. Page 45.

The Committee should conclude that — consistent with the Common Rule — organ donor intervention research must be reviewed and approved by an IRB. The Committee should develop recommendations for enhancing IRB review of such research:

- Adequate expertise among members (or engage external consultants).
- Understand usual transplant care (donor and recipient) and how research will affect that care.
- Minimization of risks.