October 26, 2016

Michael A. Carome, MD, Director
Sidney M. Wolfe, MD, Founder and Senior Advisor
Public Citizen Health Research Group
1600 20th Street, NW
Washington, DC 20009

RE: A Randomized Trial of Mild Hypothermia in Deceased Organ Donors . . .

Dear Drs. Carome and Wolfe:

This responds to your request of April 20, 2016, that the Department of Veterans Affairs (VA) Office of Research Oversight (ORO) conduct a compliance oversight investigation of the multisite research study described as "A Randomized Trial of Mild Hypothermia in Deceased Organ Donors for Protection Against Delayed Graft Function in Kidney Transplant Recipients"[1] involving the Department of Veterans Affairs (VA) Portland Health Care System (VAPORHCS).

*Public Citizen* also directed its request to the Department of Health and Human Services (HHS) Office for Human Research Protections (OHRP), as the trial (hereinafter referred to as the "Hypothermia Study") was funded by the HHS Health Resources and Services Administration (HRSA) under a grant[2] to a non-VA institution. This letter does not address *Public Citizen's* April 20 request to OHRP.

*Public Citizen* alleged that the Hypothermia Study "was unethical and failed to materially comply with key requirements of the HHS and VA regulations for the protection of human subjects," i.e., of the Federal Policy (Common Rule) for the Protection of Human Subjects, codified for HHS at Title 45 Code of Federal Regulations Part 46 (45 CFR 46) and for VA at Title 38 Code of Federal Regulations Part 16 (36 CFR 16).

Specifically, Public Citizen alleged that:

(1) The responsible institutional review board (IRB) at the trial's lead institution: (a) incorrectly determined that the trial's kidney transplant recipients were not human research subjects under the human subject protection regulations, and thus (b) failed to review and approve the trial in accordance with the regulatory criteria for approval of human subject research at 45 CFR 46.111 and 38 CFR 16.111.

(2) As a result of (1), the investigators failed to obtain the informed consent of the trial's organ-recipient subjects as required under 45 CFR 46.116 and 38 CFR 16.116.

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[1] Niemann, CU, et al. Therapeutic hypothermia in deceased organ donors and kidney-graft function. *New England Journal of Medicine (2015) 373: 405-414. DOI: 10.1056/NEJMoa1501969.*

[2] Niemann, CU, et al. The effect of therapeutic hypothermia on deceased donor renal graft outcomes – A randomized controlled trial from the Region 5 donor management controls workgroup. *Health Resources and Services Administration (2011), R38 OT22183. ClinicalTrials.gov (NCT01680744).*

ORO initiated a compliance oversight review immediately upon receipt of the allegations from Public Citizen. ORO notes that its oversight authority is limited to VA research and to the activities of VA employees in their conduct of VA research. Research conducted by non-VA entities falls outside ORO's authority. Consequently, ORO's review extended only to VA's participation in the Hypothermia Study.

In evaluating Public Citizen's complaint, ORO reviewed relevant documentation provided by VAPORHCS in response to the allegations and interviewed the VA investigator, who served as the Co-Principal Investigator (Co-PI) for the Hypothermia Study. As Co-PI, the VA investigator exercised substantive responsibilities related to study design, data analysis and integrity, manuscript preparation, and publication decisions.[3] ORO also reviewed documents provided by HRSA through OHRP.

**OVERVIEW OF THE HYPOTHERMIA STUDY**

The Hypothermia Study was "a prospective, randomized, controlled trial in two large organ donation service areas to test the potential benefit and safety of targeted hypothermia in donors with respect to rates of delayed graft function among the recipients of their kidneys."[4] Following neurologic death, organ donors were randomly assigned to "mild hypothermia" (34°C to 35°C) or "normothermia" (36.5°C to 37.5°C) temperature management groups. The study's "primary outcome was delayed graft function in the kidney recipients, which was defined as the requirement for dialysis during the first week after transplantation." [5]

The published report of Hypothermia Study findings stated that the grantee institution's IRB deemed the study "to represent nonhuman subjects research," concluded that the study "posed minimal risks to the organ recipients," and did not require informed consent from organ recipients.[6]

The Hypothermia Study was funded by HRSA on September 1, 2011, and began subject enrollment in March 2012. In July 2012, the Hypothermia Study Co-PI, who operated the study's Southern California Coordinating Center, accepted a position as a staff surgeon at VAPORHCS.

The newly hired VA investigator promptly submitted an application to continue Hypothermia Study activities at VAPORHCS. In submitting the VAPORHCS research application, the VA investigator specifically stated that he was the "primary researcher/co-PI on the grant . . . ."[7] The HRSA grant application, submitted as part of the VAPORHCS research application, indicated that the investigator would "provide primary management and oversight of all activities in Southern California related to this grant . . . ."[8]

The VAPORHCS research application specified that the VA investigator's activities would include operating the study's Southern California Coordinating Center, analyzing de-identified data from the study's organ donors and recipients, monitoring safety data, drafting reports, maintaining the United Network for Organ Sharing (UNOS) Region 5 Donor Management database (consisting of de-identified data), and performing administrative activities for the organ procurement organization (OPO) in Southern California.

Based on the description of activities provided in the investigator's application, the VAPORHCS Research

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[3] Niemann, et al. *(2015),* Supplementary Appendix to: Therapeutic hypothermia in deceased organ donors and kidney-graft function.

[4] Niemann, et al. *(2015), p 406.*

[5] Niemann, et al. *(2015), p 405.*

[6] Niemann, et al. *(2015), p 406.*

[7] Email communication from VA Investigator to Research Service, VA Portland Health Care System (VAPORHCS), July 24, 2012, 4:17 PM.

[8] Niemann, et al. *(2011),* Budget justification.

Service concluded that the VA component of the study did not involve human research subjects and, in accordance with VA requirements,[9] referred the application to the VAPORHCS Research and Development Committee (R&DC) for review.

The R&DC approved the VA investigator's Hypothermia Study activities on August 8, 2012, with the understanding that (a) the investigator (and members of the investigator's VA research team) would have no direct contact with the study's organ donors or organ recipients, (b) all clinical data related to the deceased organ donors and the renal transplant recipients would be de-identified as to the VA research team, and (c) VA personnel would not (i) obtain any data through interaction or intervention with living individuals, (ii) play any role in any clinical aspects of the study, (iii) access protected health information (PHI) or other identifiable private information of individuals involved in the study, or (iv) obtain informed consent for participation in the study.

The VA investigator's Hypothermia Study activities were supported by a subaward from the grantee institution to the Portland VA Research Foundation.

**VA FACILITY RESPONSE TO THE ALLEGATIONS**

VAPORHCS[10] indicated that although it operates a full-service kidney transplant program (which provides transplant services for Veterans from approximately 20 states) the Hypothermia Study's VA investigator did not (and does not) have a formal clinical or research role in the VAPORHCS kidney transplant program. Rather, the VA investigator serves as Director of the Surgical Intensive Care Unit where transplant patients typically receive treatment after surgery.

VAPORHCS stated that no kidneys were solicited or recovered for the Hypothermia Study from donors at VAPORHCS. VAPORHCS further stated that upon recovery, kidneys donated for the Hypothermia Study (none of which were obtained at VAPORHCS) were posted on DonorNet, from which they would be available for transplant through UNOS.[11] VAPORHCS emphasized that it "had no direct involvement with any clinical aspect of the Hypothermia Study, except for the possible random chance that a kidney listed on Donor Net" and managed under the Hypothermia Study happened to be accepted for transplant at VAPORHCS. Because the VA investigator had no access to identifiable information about these recipients, VAPORHCS could not determine whether any patients at VAPORHCS (or any other VA medical center) had received Hypothermia Study organs.[12]

The VA investigator[13] asserted that deceased organ donor research (of which the Hypothermia Study was an example) is unique from a regulatory perspective in that the only research intervention occurs in a deceased individual and is completed prior to transplantation of the deceased individual's organ(s) into the living recipient, which takes place for purely clinical purposes.

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[9] VHA Handbook 1200.01 §10.c, *Research and Development (R&D) Committee,* and VHA Handbook 1200.05 §4.l., *Requirements for the Protection of Human Subjects in Research.*

[10] Memorandum from Acting Director, VA Portland Health Care System (VAPORHCS), to Director, Human Research Protections, VHA Office of Research Oversight (ORO)(10R), April 28, 2016.

[11] UNOS' electronic network allows transplant professionals to register candidates on the national waiting list, match them with donated organs, and enter medical data on candidates, donors, and recipients. A key system application, DonorNet®, electronically records key information about donor offers and sends it to transplant hospitals with compatible candidates *(see https://www.unos.org/data/technology-for-transplantation/).*

[12] Memorandum from Acting Director, April 28, 2016.

[13] VA Investigator, Oral and written statements to ORO, May 4, May 6, and May 20, 2016.

The VA investigator[14] maintained that all members of the Hypothermia Study research team were entirely separate from the clinical teams that received and transplanted donated organs. The usual procedures of the clinical transplant teams were never altered due to the research. The research team did not interact or intervene directly with recipients and received only de-identified clinical information about recipients. No "extra" information was collected from recipients beyond that which was clinically necessary and routinely recorded. All such information was de-identified, so the VA Hypothermia Study investigator and members of the VA research team never had access to PHI or any other individually identifiable private information and had no way of knowing who had received organs from the study.

The VA investigator[15] noted that, prior to the Hypothermia Study, clinical transplant teams were not routinely notified when donor organs had been subjected to research interventions. In contrast, the Hypothermia Study investigators went to great lengths to engage the transplant community in discussions about the study prior to its initiation.

Specifically, the VA investigator stated that the Hypothermia Study investigators not only received authorization from their IRBs, but also from "the advisory boards of the two participating OPOs, the transplant programs in UNOS Region 5 (Southwest US), UNOS administration, and HRSA (the funding agency)."[16] Information about the study was posted on the national UNOS Transplant Pro website with a two-week comment period prior to study initiation, and ongoing enrollment and safety data were presented to the UNOS Region 5 Research Committee, which was created to provide oversight of the Hypothermia Study and possible future transplant studies.

The VA investigator stressed that study information documents were provided with every offer of organ availability "so transplant programs could make an informed decision on behalf of their recipients regarding the CLINICAL APPROPRIATENESS of accepting an organ from a donor enrolled in the [Hypothermia] study."[17]

The VA investigator explained that, because such a large volume of information related to organ-specific risk factors is provided when a clinical transplant team is notified of organ availability, the transplant team must routinely make decisions regarding what information to convey to the recipient based on the team's relationship with the recipient and its understanding of the recipient's wishes. According to the VA investigator, organ recipients vary considerably as to the type and amount of information they want to receive, but can always elect to avoid accepting what they, or their clinical team, consider to be high risk organs.[18]

The VA investigator indicated that HRSA personnel responsible for funding and overseeing the Hypothermia Study were fully aware of and supported the view that the study (a) did not constitute human subjects research, (b) involved only minimal risk, and (c) did not require informed consent from organ recipients. The investigator indicated that an expert panel[19] convened by HRSA in 2013 came to similar conclusions and that the National Academy of Medicine (formerly known as the Institute of Medicine) is currently planning a study to examine the unique ethical and regulatory challenges related to deceased donor intervention research.

**FINDINGS**

[14] VA Investigator, May 6, 2016.
[15] VA investigator, May 20, 2016.
[16] VA investigator, May 4, 2016. Also see Niemann, et al. *(2015), Supplementary Appendix.*
[17] VA investigator, May 4, 2016.
[18] VA investigator, May 20, 2016.
[19] VA investigator, May 4, 2016. According to the investigator, the panel was originally named the "Donor Management Research Consensus Conference" but the name was later changed to "Donor Research Expert Panel."

**A. ACTIVITIES CONSTITUTING VA RESEARCH.** ***VHA Handbook 1200.01 §3.b. VA Research.*** *VA research is research conducted by VA investigators (serving on compensated, work without compensation (WOC), or Intergovernmental Personnel Agreement (IPA) appointments) while on VA time, utilizing VA resources (e.g. equipment), or on VA property . . . .*

**Finding A(1).** ORO found that the VA Investigator played an initial central role in developing the Hypothermia Study research protocol prior to coming to VA and a continuing central role in implementing the Hypothermia Study research protocol after arriving in VA. For example:

- The VA investigator "contributed equally" with the principal investigator (PI) to the New England Journal of Medicine (NEJM) article reporting results of the Hypothermia Study.[20]
- The VA investigator was listed as the "Principal Researcher" and "Corresponding Author" for the entire research protocol (not just the VA-approved portion of the study).[21]
- As a Corresponding Author, the VA investigator (along with the PI) co-signed an "Author's Reply" stating: "We would emphasize that delayed graft function in the renal-allograft recipients was always a planned outcome variable."[22]
- The Supplementary Appendix to the NEJM article reporting results of the Hypothermia Study listed the VA investigator (along with the PI) as responsible for "Study design."[23]
- The Supplementary Appendix to the NEJM article listed the VA investigator (co-PI) as PI for the OPO in Southern California[24] (thereby fostering protocol adherence through interaction with organ donor sites).
- The Study Protocol stated that the VA investigator and the Study PI (a) were responsible for randomizing donors using an online software tool, and (b) effecting a protocol change to "focus on the actual graft outcome of interest" (i.e., delayed graft function) rather than on one of its surrogates.[25]
- The Supplementary Appendix to the NEJM article listed the VA investigator as a contact for questions from any "transplant center and surgeon [i.e., those performing direct intervention on the organ recipients] . . . concerning donor enrollment and the implications for organs offered for transplantation,"[26] (thereby fostering protocol adherence through interaction with transplant surgeons).

**B. Activities Constituting Human Subject Research.** ***VA Regulations at 38 CFR 16.102(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 . . . manipulations of the subject or the subject's environment that are performed for research purposes. . . .* [27]

**Finding B(1).** ORO found that the use of targeted hypothermia in the Hypothermia Study constituted an experimental intervention.

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[20] Niemann, et al. *(2015), p 405, footnote.*

[21] Niemann, et al. *(2015),* Protocol for: Therapeutic hypothermia in deceased organ donors and kidney-graft function.

[22] Niemann, CU & Malinoski, D. Correspondence: Therapeutic hypothermia in deceased organ donors and kidney-graft function. *New England Journal of Medicine (2015) 373: 2687. DOI: 10.1056/NEJMc1511744.*

[23] Niemann, et al. *(2015),* Supplementary Appendix, p 6.

[24] Niemann, et al. *(2015),* Supplementary Appendix, p 4.

[25] Niemann, et al. *(2015),* Protocol for: Therapeutic hypothermia in deceased organ donors and kidney-graft function.

[26] Niemann, et al. *(2015),* Supplementary Appendix, p 8.

[27] 38 CFR 16.102(f)*, Protection of Human Subjects [Federal Common Rule];* VHA Handbook 1200.05 §§ 4.l, 4.p, and 4.q., *Requirements for the Protection of Human Subjects in Research.*

- Per the published report, transplantation of donor kidneys subjected to hypothermia was considered experimental: "Current protocols stipulate that normothermia . . . be maintained in organ donors. The effect of targeted hypothermia as an intervention to protect renal function during the donation process is uncertain."[28]

**Finding B(2).** ORO found that the Hypothermia Study protocol was specifically designed to investigate the uncertain effects of targeted hypothermia on graft function among recipients of donated kidneys.

- The grant application for the Hypothermia Study listed as Objective 2: "Leverage an existing research infrastructure and regional web portal that allows for . . . the collection of recipient outcome data for the purposes of collaborative research . . . ."[29]
- The published report of the Hypothermia Study described it as a "prospective, randomized, controlled trial in two large organ-donation service areas to test the potential benefit and safety of targeted hypothermia in donors with respect to rates of delayed graft function among the recipients of their kidneys."[30]
- As there would be no benefit or safety consideration of targeted hypothermia on the organ donors, the testing of potential benefit and safety was clearly in relation to the organ recipients.
- The published report further stated that the "primary outcome, delayed graft function (the recipient's requirement for dialysis during the first week after transplantation), was determined for each kidney recipient at the center where the organ was transplanted." [31]
- The study's reported outcome was that hypothermia "had a statistically and clinically significant protective effect on renal-graft outcomes in recipients."[32]

**Finding B(3).** ORO found that the organ transplant recipients about whom the VA investigator obtained data were human research subjects under VA regulations.

- VA regulations (see Reference above) define Human Subject as a living individual about whom an investigator conducting research "obtains (1) data through intervention or interaction with the individual" where intervention may include "manipulations of the subject . . . for research purposes."
- ORO noted that "intervention" need not to occur through direct interaction with an individual but can be accomplished by indirect manipulation of the individual for research purposes.
- ORO found that protocol-dictated temperature management (hypothermia versus normothermia) of donor organs constituted indirect manipulation of (i.e., intervention with) the recipients of those organs.

As indicated previously, ORO's findings and determinations apply only to VA research and VA investigators. ORO has no authority to make findings and determinations regarding the activities of non-VA institutions or agencies.

**CONCLUSIONS**

ORO concluded that VAPORHCS (a) should have considered Hypothermia Study organ recipients to be human research subjects, and (b) should have referred the VA Investigator's research study application to the

[28] Niemann, et al. *(2015), p 406.*
[29] Niemann, et al. *(2011), p 17*.
[30] Niemann, et al. *(2015), p 406.*
[31] Niemann, et al. *(2015), p 407.*
[32] Niemann, et al. *(2015), p 411.*

VAPORHCS IRB for review.

The argument that the VA investigator did not directly intervene or interact with living individuals merely begs the question and misapplies the Common Rule which defines a Human Subject as a living individual about whom an investigator conducting research obtains "data through intervention or interaction with the individual."

Although the VA Hypothermia Study investigator had no "direct" intervention or interaction with transplant recipients, the investigator's indirect intervention on living individuals (through the study protocol) accompanied by data collection constituted human subject research.

**ORO noted that the VA investigator and the VAPORHCS R&DC appeared to have acted entirely in good faith in determining that VA Hypothermia Study activities did not constitute human subject research.**

Such had been the determination of the grantee institution's IRB, and the HHS awarding agency appeared to have at least tacitly agreed with this determination. In addition, the VA investigator consulted widely with transplant organizations and members of the transplant community in developing and implementing the Hypothermia Study, and ensured that transplant teams were provided with full information about the Hypothermia Study and study organs made available for transplant.

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, and specifically regarding the status as potential research subjects of the recipients of experimentally treated organs.[33]

For example, a recent survey of transplant surgeons, OPO professionals, and IRB members "found wide variations in their perceptions about research classification, risk assessment for donors and organ transplant recipients, regulatory oversight requirements, and informed consent in the context of deceased donor intervention research."[34]

Nevertheless, bioethicists have argued that recipients of organs from donor interventions (and recipients of organs from control donors) "are no less 'human research subjects' than are recipients of blood products, bioprosthetic devices, or pharmaceuticals that have been randomly assigned to one or another preparative intervention" and noted that "although it might be argued that direct intervention occurs only in donors, recipients are also affected by manipulations of donor care."[35]

While the above article explored the question of whether a waiver of recipient informed consent might be justified, the article nonetheless firmly concluded that deceased donor intervention research involved human subjects research that was required under the Common Rule to undergo IRB review/approval (with subsidiary considerations about informed consent waivers).

However, given the widespread uncertainty within the transplant community, ORO acknowledges that other

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[33] Glazier, AK, et al. A framework for conducting deceased donor research in the United States. *Transplantation (2015) 99(11): 2252-2257.*

[34] Rodrigue, JR, et al. Deceased donor intervention research: A survey of transplant surgeons, organ procurement professionals, and institutional review board members. *American Journal of Transplantation (2016) 16(1): 278-286.*

[35] Rey MM, et al. Informed Consent in Research to Improve the Number and Quality of Deceased Donor Organs. *Critical Care Medicine (2011),* 39(2):280-283. DOI: 10.1097/CCM.0b013e3181feeb04.

federal agencies may well come to different conclusions regarding application of the Common Rule to their deceased organ donor intervention research.

Such uncertainty presents unacceptable vulnerabilities for everyone involved in transplant research, including especially the recipients of organs affected by deceased donor intervention studies. Also vulnerable, from a regulatory (and perhaps legal) perspective, are the surgeons who knowingly take part in a research protocol by transplanting organs that have been subjected to experimental conditions, whether or not the surgeons have had any role in designing the research or any interest in the results of the research.

Consequently, ORO will work with HHS and other interested Common Rule agencies to develop consensus guidelines for application of federal human research protection standards to deceased donor intervention research.

**OFFICE OF RESEARCH OVERSIGHT**

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John Thomas Puglisi, PhD
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