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April 20, 2016

Jerry Menikoff, M.D., J.D.
Director
and
Kristina Borrer, Ph.D.
Director, Division of Compliance Oversight
Office for Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

J. Thomas Puglisi, Ph.D.
Chief Officer
Office of Research Oversight (10R)
Veterans Health Administration
Department of Veterans Affairs
810 Vermont Avenue, NW
Washington, DC 20420

Re: A Randomized Trial of Mild Hypothermia in Deceased Organ Donors for Protection Against Delayed Graft Function in Kidney Transplant Recipients

Funding: Health Resources and Services Administration, Grant #R38OT22183

Principal Investigators: Claus Niemann, M.D., University of California, San Francisco, and Darren Malinoski, M.D., Portland VA Medical Center and Oregon Health & Science University

ClinicalTrials.gov Identifier: NCT01680744

Dear Drs. Menikoff, Borrer, and Puglisi:

Public Citizen, a consumer advocacy organization with more than 400,000 members and supporters nationwide, hereby requests that the Office for Human Research Protections (OHRP) and the Department of Veterans Affairs' (VA's) Office of Research Oversight (ORO) immediately launch a joint compliance oversight investigation into the above-referenced clinical trial and appropriately sanction all institutions engaged in the trial for failing to protect the human subjects who were enrolled unwittingly in the research. The trial was funded by the Department of Health and Human Services (HHS) through a grant from the Health Resources and Services Administration (HRSA) and was conducted, in part, by the VA through the involvement of Dr. Malinoski, a co-principal investigator of the trial who is employed by the

Portland VA Medical Center.¹ Thus, both the OHRP and the VA's ORO have jurisdiction over this research.

Under the trial protocol, 572 patients undergoing cadaveric kidney transplantation received kidneys from deceased donors who had been randomly assigned at the time of declaration of brain death (hereafter referred to as brain-dead donors) to either normothermia (body temperature maintained at 36.5 to 37.5°C; usual-care control intervention; 287 subjects) or mild hypothermia (body temperature maintained at 34 to 35°C; experimental intervention; 285 subjects) prior to removal of the donor organs.² The primary research outcome determined for each subject was delayed graft function, which was defined as the patient requiring dialysis during the first week after transplantation.³

A review of the *New England Journal of Medicine (NEJM)* article presenting the trial's results⁴ reveals that the trial, as conducted, was unethical and failed to materially comply with key requirements of the HHS and VA regulations for the protection of human subjects at 45 C.F.R. Part 46 and 38 C.F.R. Part 16, respectively. In particular:

- (1) The institutional review board (IRB) at the University of California, San Francisco (UCSF), the lead institution for the trial, determined — incorrectly — that the research represented “nonhuman subjects research under U.S. federal law, since the patients were deceased.”⁵ This determination represents a disturbing failure of the UCSF human subjects protection system.
- (2) As a result of (1), the trial investigators failed to obtain the informed consent of the subjects of the trial, in violation of the basic ethical principle of respect for persons articulated in the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research's 1979 report, *Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (widely known as the Belmont Report),⁶ and in violation of the requirements of the human subjects protection regulations at 45 C.F.R. § 46.116 and 38 C.F.R. § 16.116.

¹ Supplementary Appendix for: 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.
http://www.nejm.org/doi/suppl/10.1056/NEJMoa1501969/suppl_file/nejmoa1501969_appendix.pdf. Accessed April 1, 2016.

² 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.

³ *Ibid.*

⁴ *Ibid.*

⁵ *Ibid.*

⁶ National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. April 18, 1979.
<http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>. April 9, 2016.

- (3) As a result of (1), although the UCSF IRB “evaluated” the trial,⁷ it apparently failed to review and approve the trial in accordance with the requirements of the human subjects protection regulations at 45 C.F.R. § 46.111 and 38 C.F.R. § 16.111.

The following discussion explains in detail the basis for our complaint and raises issues and questions that should be addressed during your investigation of this trial.

Overview of the trial

Trial rationale and primary objective

Delayed graft function is a significant problem in renal transplantation, occurring in up to 50 percent of patients receiving kidney transplants recovered from brain-dead donors.⁸ It results in increased health care costs and decreased long-term function of transplanted kidneys.⁹

In their *NEJM* article, Dr. Niemann, Dr. Malinoski, and their co-authors provided the following background information regarding use of hypothermia prior to removal of kidneys from brain-dead donors:¹⁰

Therapeutic hypothermia, also termed targeted temperature management, is an established intervention that is used to protect neurologic function in patients with certain types of cardiac arrest, stroke, and asphyxia. **The effect of therapeutic hypothermia on renal protection is uncertain.** However, in a retrospective study involving patients with cardiac arrest, mild hypothermia appeared to protect against renal injury. An experimental study involving rabbits showed that rapid cooling to moderate hypothermia preserved renal function during cardiac arrest. A review article summarized the mechanisms for benefit with hypothermia; these include reduced metabolism and reduction of free-radical production.

Current [renal transplantation] protocols stipulate that normothermia, which frequently requires active warming, be maintained in organ donors. **The effect of targeted hypothermia as an intervention to protect renal function during the donation process is uncertain.**

[Emphasis added]

The primary objective of the trial was “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.**” [Emphasis added]¹¹

⁷ 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.

⁸ *Ibid.*

⁹ *Ibid.*

¹⁰ *Ibid.*

¹¹ *Ibid.*

Importantly, before the trial began, although the investigators had reason to believe that targeted mild hypothermia in brain-dead donors might improve renal outcomes in patients receiving kidney transplants, the range of potential outcomes for the experimental group subjects included both a decreased and an increased rate of delayed graft function compared with control group subjects.

Trial design

From March 2012 to October 2013, the investigators randomly assigned 394 brain-dead organ donors to either normothermia or mild hypothermia prior to removal of the donor organs.¹² Donors randomly assigned to the normothermia control group were kept warm to maintain a body temperature of 36.5 to 37.5°C,¹³ which the trial protocol characterized as “current standard practice, demonstrated by the data reported from a random sample of 80 donors from CTDN [California Transplant Donor Network] in 2010.”¹⁴

Donors randomly assigned to the mild hypothermia experimental group either were allowed to spontaneously reach a body temperature of 34 to 35°C or were cooled with the use of forced-air systems or passive cooling devices.¹⁵

Following randomization of donors, the goal was to reach the target temperature within four hours of donor enrollment. Once the assigned target was reached, temperature was maintained within the goal range until the donor was transported to the operating room for organ removal.¹⁶ The protocol stipulated that the duration of mild hypothermia should be at least 12 hours.¹⁷

A total of 572 patients undergoing kidney transplantation were enrolled in the trial: 287 subjects participated in the control group and received kidneys from donors who were assigned to normothermia management, and 285 subjects participated in the experimental group and received kidneys from donors who were assigned to mild hypothermia management.¹⁸

¹² *Ibid.*

¹³ *Ibid.*

¹⁴ Protocol for: 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. http://www.nejm.org/doi/suppl/10.1056/NEJMoa1501969/suppl_file/nejmoa1501969_protocol.pdf. Accessed April 1, 2016.

¹⁵ 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.

¹⁶ Supplementary Appendix for: 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. http://www.nejm.org/doi/suppl/10.1056/NEJMoa1501969/suppl_file/nejmoa1501969_appendix.pdf. Accessed April 1, 2016.

¹⁷ Protocol for: 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. http://www.nejm.org/doi/suppl/10.1056/NEJMoa1501969/suppl_file/nejmoa1501969_protocol.pdf. Accessed April 1, 2016.

¹⁸ 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.

The primary research intervention that was tested in the trial was transplantation of kidneys from brain-dead donors managed with hypothermia. The primary research outcome, delayed graft function, was determined for each subject at the center where the organ was transplanted.¹⁹ The investigators also collected the following data for the subjects: age, sex, body mass index, serum post-transplantation creatinine levels, post-transplantation urine output, and postoperative complications.^{20,21}

Failure to recognize trial as involving human subjects research

The HHS and VA human subjects protection regulations at 45 C.F.R. § 46.102(f) and 38 C.F.R. § 16.102(f), respectively, define a *human subject*, in part, as follows:

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.

In their *NEJM* article, the trial investigators reported the following:²²

The study was evaluated by the institutional review board at the University of California, San Francisco, and was **deemed to represent nonhuman subjects research under U.S. federal law, since the patients were deceased.** [Emphasis added]

Although the brain-dead donors involved in the trial were deceased and therefore not human subjects of the trial, the patients who received kidneys from these donors clearly were human

¹⁹ *Ibid.*

²⁰ *Ibid.*

²¹ Protocol for: 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. http://www.nejm.org/doi/suppl/10.1056/NEJMoa1501969/suppl_file/nejmoa1501969_protocol.pdf. Accessed April 1, 2016.

²² 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.

subjects: They were living individuals about whom the investigators conducting this research obtained both data through an intervention with the individuals and identifiable private information.

The primary research intervention that was tested in the trial was transplantation of kidneys from brain-dead donors managed with hypothermia, a procedure that did not represent usual care. This procedure involved manipulation of the patient's kidney transplantation procedure for research purposes. Following this intervention, the investigators obtained data on the patients' transplanted kidney outcomes.

Furthermore, the investigators' collection of data regarding the patients' body mass index and need for hemodialysis, serum creatinine levels, urine output, and complications post-transplantation constituted obtaining identifiable private information about living individuals.

The fact that the trial represented human subjects research should have been immediately obvious to anyone with even a basic understanding of federal human subjects protection regulations. And yet, remarkably, the UCSF IRB determined that the trial represented non-human-subjects research. This determination represents a major failure of the UCSF human subjects protection system. As a result of this failure, the trial failed to comply with key requirements of the HHS and VA human subjects protection regulations, and the human subjects enrolled in the trial were not afforded the important protections that they deserved.

Failure to satisfy informed consent requirements

The trial investigators failed to obtain and document the informed consent of the human subjects who, therefore, were enrolled unwittingly in the trial. In their *NEJM* article, the investigators stated the following:²³

Furthermore, the institutional review board concluded that this study posed minimal risks to the organ recipients and that informed consent would not be required for a recipient to accept an organ from a donor enrolled in the study.

The failure to obtain the informed consent of the transplant patients who were the subjects of the trial violated the Belmont Report's basic ethical principle of respect for persons.²⁴

Furthermore, the trial was not eligible for a waiver of the requirement for obtaining the informed consent of all subjects, and the conduct of the trial, therefore, failed to comply with the requirements of the HHS and VA human subjects protection regulations at 45 C.F.R. § 46.116 and 38 C.F.R. § 16.116, respectively.

²³ *Ibid.*

²⁴ National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. April 18, 1979. <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>. Accessed April 9, 2016.

The HHS and VA human subjects protection regulations at 45 C.F.R. § 46.116(d) and 38 C.F.R. § 16.116(d), respectively, stipulate that an IRB may waive the requirements to obtain informed consent of human subjects provided it finds and documents that:

- (1) The research involves no more than minimal risk to the subjects;
- (2) The waiver will not adversely affect the rights and welfare of the subjects;
- (3) The research could not practicably be carried out without the waiver; and
- (4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

The UCSF IRB apparently addressed only the first of the above four findings required for granting a waiver of the requirements for obtaining informed consent. Whether the trial *a priori* involved no more than minimal risk to the subjects is debatable given that (a) the effect — positive or negative — of the kidney donor hypothermia management on the transplant patients who were the subjects of the trial was uncertain before the trial began, and (b) the purpose of the trial was 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.

Nevertheless, even if it was reasonable to conclude that the trial involved no more than minimal risk to the subjects, it would have been very practicable for the investigators to carry out the trial without a waiver of the informed consent requirements. Therefore, the trial failed to satisfy the third requirement for waiver of informed consent under the HHS and VA human subjects protection regulations.

Apparent failure to satisfy requirements for IRB review and approval

As previously noted, in their *NEJM* article, the trial investigators reported that the UCSF IRB “evaluated” the trial. Evaluating a trial is not the same as reviewing and approving it in accordance with the requirements of the HHS and VA human subjects protection regulations at 45 C.F.R. § 46.111 and 38 C.F.R. § 16.111, respectively, which require that the IRB determine that *all* of the following criteria are satisfied prior to approving research:

- (1) Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
- (2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.
- (3) Selection of subjects is equitable.

- (4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 45 C.F.R. § 46.116 and 38 C.F.R. § 16.116, respectively.
- (5) Informed consent will be appropriately documented, in accordance with, and to the extent required by 45 C.F.R. § 46.117 and 38 C.F.R. § 16.117, respectively.
- (6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
- (7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
- (8) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

As previously noted, the UCSF IRB failed to ensure that criteria (4) and (5) above were satisfied for the trial. Furthermore, given the apparent failure of the UCSF IRB to review and approve the trial, the other requirements for IRB review and approval also were not satisfied.

Conclusions and requested actions

In closing, the trial, as conducted, was unethical and failed to materially comply with key requirements of the HHS and VA regulations for the protection of human subjects at 45 C.F.R. Part 46 and 38 C.F.R. Part 16, respectively. It is therefore imperative that the OHRP and the VA's ORO launch a joint compliance oversight investigation of the trial and appropriately sanction all institutions engaged in the trial for failing to protect the human subjects who were enrolled unwittingly in the research.

In conducting this investigation, the OHRP and VA's ORO should address the following questions and issues, among others:

- (1) Did the trial investigators represent the research as not involving human subjects in correspondence submitted to the UCSF IRB? If so, what rationale did the investigators offer in making those representations, and did the representatives of the IRB raise any objections in response?
- (2) What process did the UCSF IRB employ when it evaluated the trial? Did the IRB chairperson, another member of the IRB, a quorum of the IRB at a convened meeting, or an IRB administrative staff member conduct this evaluation? (We note that the trial did

not meet the criteria for any of the categories of research that may be reviewed by the IRB through an expedited review procedure.²⁵)

- (3) Did the IRBs at any of the other transplant centers engaged in the trial (i.e., hospitals where kidneys recovered from trial donors were transplanted into the subjects) review or consider reviewing the trial? If so, what were the outcomes of those reviews?
- (4) The trial protocol characterized the management of donors randomly assigned to the normothermia control group as “current standard practice, demonstrated by the data reported from a random sample of 80 donors from CTDN [California Donor Transplant Network] in 2010.”²⁶ The fact that the trial investigators relied on a random sample of donors from the CTDN in 2010 to demonstrate current standard practice raises questions about whether the normothermia management was universally practiced for all donors from the CTDN at the time the trial was conducted. This issue is important because if maintaining brain-dead donors at normothermia was not a universal practice, then the trial protocol also may have altered the care delivered to kidney transplant patients enrolled as subjects in the normothermia control group and exposed those subjects to risks. Therefore, what were the results of the analysis of donor body temperature management for the random sample of 80 donors from the CTDN in 2010? How do these results compare to an analysis of donors from the CTDN during the several months immediately prior to the initiation of the trial in March 2012?
- (5) The trial protocol stipulated that the duration of mild hypothermia should be at least 12 hours. Did this protocol stipulation cause any delay in recovery of organs from any of the hypothermia experimental group donors? If so, was there any evidence before or during the trial that such delays could have had an adverse impact on kidney outcomes in patients who received kidney transplants from these donors?
- (6) The final statistical analysis plan provided with the trial protocol stated the following:²⁷

The donor hypothermia trial was designed to enroll a maximum of 500 donor subjects, resulting in up to 1,000 transplanted kidneys. The primary outcome for the trial is delayed graft function (DGF), defined as the need for renal dialysis within the first week post-transplantation. The original trial design specified two interim data analyses, to occur approximately one-third and two-thirds of the way through the trial. However, the trial enrolled subjects more rapidly than anticipated so, at the specified time for the first interim analysis, approximately two-thirds of the subject population had been enrolled.

²⁵ 63 FR 60364-60367. Department of Health and Human Services. Protection of human subjects: Categories of research that may be reviewed by the institutional review board (IRB) through an expedited review procedure. <https://www.gpo.gov/fdsys/pkg/FR-1998-11-09/pdf/98-29749.pdf>. Accessed April 5, 2016.

²⁶ Protocol for: 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. http://www.nejm.org/doi/suppl/10.1056/NEJMoa1501969/suppl_file/nejmoa1501969_protocol.pdf. Accessed April 1, 2016.

²⁷ *Ibid*.

The failure to conduct the first interim analysis as stipulated in the trial design represented a failure to ensure that risks to the subjects were minimized. Why did the investigators not suspend trial enrollment one-third of the way through the trial and allow the first interim analysis to be completed, as stipulated in the protocol design, before deciding whether to continue enrollment?

(7) The summary of changes in the final protocol stated the following:²⁸

Enrollment of the trial was approximately delayed by 6 months. This was due to initial concerns by risk management and legal council [sic] at several major transplant centers in region 5. The investigators felt strongly that endorsement from all transplant centers is of paramount importance to the success of the trial. As such, Drs Niemann and Malinoski spent considerable time with these transplant centers on education.

Did risk management staff and legal counsel at any of these major transplant centers raise concerns about the determinations of the UCSF IRB that the trial represented nonhuman subjects research, that the trial posed minimal risks to the organ recipients, and that informed consent therefore would not be required for the transplant recipients? If so, how many transplant centers raised such concerns, and what was the response from the co-principal investigators? Did any major transplant center refuse to participate because of unresolved concerns?

Finally, we urge the OHRP and the VA's ORO to immediately take the following additional actions:

- (1) Require that the trial investigators develop and implement a plan for contacting all human subjects enrolled in the trial (or the next of kin for any deceased subjects) and communicating in writing a detailed notification of the subjects' participation in the trial without their voluntary informed consent. The plan, including the proposed content of the notification, should be reviewed and approved by the IRB for each institution engaged in the trial and by the OHRP and the VA's ORO. The final plan and content of a sample notification should be made available to the public. The written notification should include:
 - (a) A statement that the trial involved human subjects research, an explanation of the purposes of the research, a description of the procedures that were followed, and identification of the procedures that were experimental (i.e., transplantation of kidneys from organ donors managed with mild hypothermia).
 - (b) A description of the reasonably foreseeable risks or discomforts to the subjects.
 - (c) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.

²⁸ *Ibid.*

- (d) An explanation of whom to contact for answers to questions about the research and research subjects' rights.
 - (e) A statement that the research failed to comply with applicable federal regulations for the protection of human subjects, including requirements for IRB review and approval and for obtaining and documenting the voluntary informed consent of the subjects.
- (2) Determine whether HHS or the VA is currently funding or conducting any ongoing trials that involve experimental manipulation of donor organs before or after removal from the donor and the subsequent assessment of clinical outcomes in transplant patients who receive such organs. For any such trials, confirm whether the research is being conducted in accordance with all applicable federal human subjects protection regulations, including requirements for IRB review and approval and for obtaining and documenting the informed consent of the subjects. For any such trials not in compliance with all requirements of applicable federal human subjects protection regulations, invoke your regulatory authority and suspend the trials.

Please note that the OHRP and the VA's ORO may share our complaint letter, with identifiers, with anyone. We will be posting a copy on Public Citizen's website as well.

Thank you for your prompt attention to this urgent matter regarding the protection of human subjects. We look forward to the OHRP's and ORO's thorough and careful investigation into this unethical trial.

Please contact us if you have any questions or need additional information.

Sincerely,



Michael A. Carome, M.D.
Director
Public Citizen's Health Research Group



Sidney M. Wolfe, M.D.
Founder and Senior Adviser
Public Citizen Health Research Group

cc: The Honorable Sylvia Mathews Burwell, Secretary of Health and Human Services
The Honorable Karen B. DeSalvo, Acting Assistant Secretary for Health, HHS
The Honorable David J. Shulkin, Under Secretary for Health, VA