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September 13, 2016

Jerry Menikoff, M.D., J.D.
Director

Kristina Borror, 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

Re: Individualized Comparative Effectiveness of Models Optimizing Patient Safety and Resident Education (iCOMPARE) Trial and Flexibility in Duty Hour Requirements for Surgical Trainees (FIRST) Trial

Dear Drs. Menikoff and Borror:

We are writing in follow-up to Public Citizen and the American Medical Student Association's (AMSA's) letters (dated November 19, 2015;[1] February 11, 2016;[2] and March 9, 2016[3]) regarding the iCOMPARE and FIRST trials. Nearly 10 months ago, we first called on the Office for Human Research Protections (OHRP) to immediately launch compliance oversight investigations into both trials, which are highly unethical and fail to materially comply with key requirements of Department of Health and Human Services (HHS) regulations for the protection of human subjects at 45 C.F.R. Part 46. We also urged OHRP to invoke its authority and immediately suspend the iCOMPARE trial, which is funded in part by the National Institutes of Health.

Disturbingly, OHRP has yet to take any of these long-overdue actions. Making matters worse, the Accreditation Council for Graduate Medical Education (ACGME) — despite being made aware of the unethical nature of the trials — extended its waiver of some of the organization's current key resident work hour restrictions and provided additional funding to allow the

[1] Public Citizen and the American Medical Student Association. Letters to OHRP regarding the iCOMPARE and FIRST trials. November 19, 2015. http://www.citizen.org/hrg2283 and http://www.citizen.org/hrg2284, respectively. Accessed September 12, 2016.
[2] Public Citizen and the American Medical Student Association. Follow-up letter to OHRP regarding the unethical iCOMPARE trial. February 11, 2016. http://www.citizen.org/hrg2302. Accessed September 12, 2016.
[3] Public Citizen and the American Medical Student Association. Second follow-up letter to OHRP regarding the unethical iCOMPARE trial. March 9, 2016. http://www.citizen.org/hrg2304. Accessed September 12, 2016.

continuation of the FIRST trial for a third academic year beginning July 1, 2016.[4] We have learned that the iCOMPARE trial has been extended for another year as well.[5]

As we noted in our November 19, 2015, letters, the failures of the FIRST trial and iCOMPARE trial investigators to obtain the informed consent of the residents and patients who are the human subjects of the research violate the Belmont Report's basic ethical principle of respect for persons.[6]

These ethical violations are thrown into sharp relief by results of a national public opinion poll, commissioned by Public Citizen and conducted by Lake Research Partners, that assessed the public's attitudes toward limits on medical resident work hours (see enclosed report). The poll, which surveyed a randomly identified representative sample of 500 likely voters nationwide, was conducted on July 20-24, 2016. In particular, we call OHRP's attention to the responses to the following question:

> Researchers are conducting an experiment at more than 100 hospitals in the U.S. The hospitals were randomly divided into two groups: In one group, first-year residents are working shifts lasting no more than 16 hours in a row, as currently required by the ACGME. In the other group, first-year residents are allowed to work shifts lasting 28 or more hours in a row without sleep. The researchers want to find out whether patients treated at the hospitals where first-year residents are allowed to work for 28 or more hours in a row are more likely to die or have serious complications compared with patients treated at hospitals where first-year residents work no more than 16 hours in row.
>
> If you were admitted to one of the hospitals participating in this experiment, would you want to be informed if that hospital was assigned to the group where first-year residents are allowed to work shifts lasting 28 or more hours in a row without sleep?

A total of 84 percent of respondents stated that they would want to be so informed, with 78 percent responding "strongly" in the affirmative. The margin of error for the poll is +/− 4.4%. Eighty-one percent of those who had been employed (or had a household member employed) in hospitals in the past five years stated that they would want to be so informed, as did 83-88% of people who had been hospitalized or visited the emergency room (or had a household member hospitalized or visit the emergency room) at least once within the previous three years.

Allowing the continued unwitting enrollment of tens of thousands of patient subjects in the FIRST and iCOMPARE trials, in the face of data showing that the vast majority of the adult public would want to be informed of this experiment if they were admitted to one of the

[4] Accreditation Council for Graduate Medical Education. Letter to members of the graduate medical education community. May 17, 2016. http://www.acgme.org/Portals/0/PDFs/Nasca-Community/NascaLettertotheCommunity-5-17-16.pdf. Accessed September 12, 2016.

[5] Personal communication with residents who have been human subjects in the iCOMPARE trial.

[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. Accessed September 12, 2016.

experimental-group hospitals, would constitute an egregious, knowing disregard for the basic ethical principle of respect for persons.

Note that simply informing patient subjects of their involvement in these experiments would not constitute voluntary informed consent as required by HHS regulations and the ethical principles governing human subjects research, nor would it address the other ethical and regulatory lapses related to the design and conduct of these trials that were described in our prior letters. Moreover, the cluster-randomization design of these trials essentially makes it impossible to obtain the voluntary informed consent of all patient subjects enrolled at hospitals assigned to the experimental arms: Subjects would be unable to refuse participation in the trials without leaving the hospital and going to another, which for many seriously ill patients would not be medically feasible.

We again call on OHRP to immediately launch formal compliance oversight investigations into the FIRST and iCOMPARE trials, appropriately sanction all institutions engaged in this unethical research, and use its legal authority to suspend the conduct of the iCOMPARE trial. OHRP also should publicly recommend that the FIRST trial be suspended. Such actions are necessary to protect patient and resident subjects from potential serious harm and to deter similar unethical research from being conducted in the future.

Further inaction by OHRP would represent a moral failure of the agency and a continued abrogation of its fundamental legal responsibility to protect human subjects.

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

Sincerely,

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Enclosure

cc: The Honorable Sylvia Mathews Burwell, Secretary of Health and Human Services
The Honorable Karen B. DeSalvo, Acting Assistant Secretary for Health
Thomas J. Nasca, M.D., M.A.C.P., Chief Executive Officer, ACGME