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Re: Individualized Comparative Effectiveness of Models Optimizing Patient Safety and Resident Education (iCOMPARE) Trial

Dear Drs. Menikoff and Borror:

We are writing in follow-up to Public Citizen and the American Medical Student Association's (AMSA's) November 19, 2015, and February 11, 2016, letters calling on the Office for Human Research Protections (OHRP) to immediately launch a compliance oversight investigation into the iCOMPARE trial, which is highly unethical and fails to materially comply with key requirements of the Department of Health and Human Services (HHS) regulations for the protection of human subjects at 45 C.F.R. Part 46. Public Citizen and AMSA also urged OHRP to invoke its authority under the OHRP-approved Federalwide Assurance (FWA) for each institution engaged in the iCOMPARE trial by immediately suspending the conduct of the trial. To our dismay, OHRP has not yet taken either action.

On February 24, Public Citizen obtained under a Freedom of Information Act request additional documents from the National Institutes of Health (NIH) that provide further evidence that the iCOMPARE trial — as designed, reviewed, and currently being conducted — violates basic ethical principles and federal regulatory requirements related to the protection of human subjects. These newly obtained documents include:

- Certification documents regarding institutional review board (IRB) review (or determinations that the trial either did not involve human subjects research or qualified

for exemption and therefore did not need IRB review) for each institution participating in the iCOMPARE trial.
- An undated plan written by the iCOMPARE investigators for monitoring serious adverse events in interns who are enrolled as subjects in the iCOMPARE trial and a related December 1, 2015, email sent by the investigators to internal medicine residency program directors at each institution participating in the iCOMPARE trial.
- Records from the Data and Safety Monitoring Board (DSMB) established by the National Heart, Lung, and Blood Institute (NHLBI) to monitor the safety of the human subjects enrolled in the iCOMPARE trial.

Most significantly, we learned from these documents that for at least 56 of the 63 internal medicine training programs participating in the iCOMPARE trial, either (1) the required IRB review did not occur because the trial was found — incorrectly — to not involve human subjects research or to involve only exempt human subjects research; or (2) when IRB review did occur, the IRBs reviewed the trial using an expedited review procedure, even though the trial did not qualify for such a review procedure. Disturbingly, we also discovered that nearly 12 weeks ago, on December 13, 2015, OHRP received from NIH these same records documenting these serious failures regarding IRB review of the iCOMPARE trial.[1]

In addition, other documents reaffirm that (1) the iCOMPARE trial involves greater than minimal risk to the first-year resident subjects; (2) the design of the trial fails to minimize risks to the subjects; and (3) the failure of the investigators to obtain the voluntary informed consent of the resident subjects violates the ethical principle of respect for persons as well as the requirements of HHS regulations at 45 C.F.R. §46.116.

Inappropriate determination that the iCOMPARE trial did not involve human subjects research

Documents provided by NIH reveal that officials at the following institutions determined that the iCOMPARE trial did not involve human subjects research and therefore did not need to comply with the provisions of HHS regulations for the protection of human subjects related to IRB review and voluntary informed consent:

- Beth Israel Deaconess Medical Center (determination made on December 9, 2014)[2]
- University of North Carolina (determination made on March 30, 2015)[3]
- University of Vermont (determination made on May 18, 2015)[4]

[1] Email from Gail Weinmann of the National Heart, Lung, and Blood Institute to several officials in the Department of Health and Human Services' Office for Human Research Protections; Subject: Requested documents on iCOMPARE. December 13, 2015. http://www.citizen.org/documents/Email_NHBLI_OHRP_iCOMPARE_Dec-13-2015.pdf. Accessed March 7, 2016.
[2] Certification documents for institutional review board review of the iCOMPARE trial. http://www.citizen.org/documents/iCOMPARE-IRB-Certification-docs.pdf. Accessed March 7, 2016. PDF pages 6-8.
[3] *Ibid*. PDF page 31.
[4] *Ibid*. PDF page 37.

These determinations represent colossal failures of the human subjects protection systems at these institutions and violations of the HHS regulations for the protection of human subjects.

HHS human subjects protection regulations at 45 C.F.R. §46.102(d) define *research* as follows:

> *Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

The iCOMPARE trial clearly meets this definition.

HHS human subjects protection regulations at 45 C.F.R. §46.102(f) 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.

Both the internal medicine residents at hospitals engaged in the iCOMPARE trial and their patients obviously are human subjects of the research. The researchers are intervening with both groups at the residency programs randomized to the experimental group by manipulating the duty schedules of the internal medicine residents — particularly, the first-year residents — for research purposes. The researchers also are interacting with the internal medicine residents through research-specific surveys and collecting identifiable private information about resident subjects at all participating programs.

Finally, officials at The George Washington University (GWU), which was randomly assigned to the experimental arm of the trial, determined on February 2, 2015, that the institution was not engaged in research-related activities involving human subjects, and thus IRB review of the iCOMPARE trial was not needed.[5] However, GWU undoubtedly is engaged in the iCOMPARE trial because investigators there are intervening for research purposes with internal medicine resident subjects and patient subjects by manipulating the duty schedules of the residents for the purposes of the experiment.

[5] *Ibid*. PDF page 14.

Inappropriate determination that the iCOMPARE trial was exempt under the HHS human subjects protection regulations

Documents provided by NIH reveal that officials at the following institutions determined that the iCOMPARE trial was exempt human subjects research under one or more of the six exemption categories specified under HHS regulations at 45 C.F.R. §46.101(b) and therefore did not need to comply with the provisions of the HHS regulations related to IRB review and voluntary informed consent:

- Atlantic Health System (determined to be exempt under exemption category 1 on November 4, 2014)[6]
- Cedars-Sinai (determined to be exempt under exemption categories 1 and 2 on March 23, 2015)[7]
- Cleveland Clinic ("**approved** under expedited review on 3/27/2015 as **Exempt Research** for the collection of data in an anonymous manner in which participants will not be identifiable nor linked to a code that could identify them" [*emphasis in original*])[8]
- Creighton University (determined to be exempt under exemption category 2 on February 12, 2015)[9]
- East Carolina University (determined to be exempt under exemption category 2 on May 18, 2015)[10]
- MedStar Health Research Institute (determined to be exempt under exemption category 1 on May 11, 2015)[11]
- University of Washington (determined to be exempt under exemption categories 1 and 2 on June 25, 2015)[12]

These determinations represent serious failures of the human subjects protection systems at these institutions and violations of the HHS regulations for the protection of human subjects.

Exemption category 1 is defined in HHS regulations at 45 C.F.R. §46.101(b)(1):

> Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

Exemption category 2 is defined in HHS regulations at 45 C.F.R. §46.101(b)(2):

> Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior,

[6] *Ibid*. PDF page 3.
[7] *Ibid*. PDF page 9.
[8] *Ibid*. PDF page 10.
[9] *Ibid*. PDF page 11.
[10] *Ibid*. PDF pages 12-13.
[11] *Ibid*. PDF page 15.
[12] *Ibid*. PDF page 38.

> unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

These exemption categories were intended to cover innocuous research studies that posed little to no risk to subjects.[13,14] The iCOMPARE trial — which involves an experimental intervention that exposes first-year internal medicine residents to work shifts of up to 28 or more hours and then measuring mortality and morbidity outcomes in their patients — far exceeds the bounds of these exemption categories because it is not innocuous research and poses significant risks.

Furthermore, with respect to exemption category 1, the trial is not limited to established or commonly accepted educational settings and normal educational practices because it also involved resident physicians as employees of hospitals and the delivery of clinical care to patients. With respect to exemption category 2, the intervention being tested at institutions randomized to the experimental group was not limited to research involving the use of educational tests, survey procedures, interview procedures, or observation of public behavior.

Inappropriate use of the expedited IRB review procedure

Documents provided by NIH reveal that the IRBs at the following institutions understood that the iCOMPARE trial involved non-exempt human subjects research, but reviewed and approved the trial using an expedited review procedure under HHS regulations at 45 C.F.R. §46.110, even though the trial was ineligible for such a review procedure:

- The University of Pennsylvania (initially approved on October 7, 2014, under expedited review categories 5 and 7; underwent continuing review and was reapproved on September 24, 2015, again under an expedited review procedure); 39 other institutions participating in the iCOMPARE trial relied upon the University of Pennsylvania's IRB reviews and approvals[15]
- Henry Ford Health System (initially approved on March 20, 2015, under an expedited review procedure based on the determination that the research involved no more than minimal risk to subjects; approval document does not specify the expedited review category used to justify the review)[16]

[13] 44 FR 47688-47729. Department of Health, Education and Welfare. Proposed regulations amending basic HEW policy for protection of human research subjects (45 CFR Part 46). August 14, 1979. http://www.hhs.gov/ohrp/archive/documents/19790814.pdf. Accessed March 7, 2016.
[14] 46 FR 8366-8392. Department of Health and Human Services. Final regulations amending basic HHS policy for the protection of human research subjects (45 CFR Part 46). January 26, 1981. http://archive.hhs.gov/ohrp/documents/19810126.pdf. Accessed March 7, 2016.
[15] Certification documents for institutional review board review of the iCOMPARE trial. http://www.citizen.org/documents/iCOMPARE-IRB-Certification-docs.pdf. Accessed March 7, 2016. PDF pages 1, 34, and 44.
[16] *Ibid*. PDF page 16.

- Presence St. Francis Hospital (initially approved on January 28, 2015, under an expedited review procedure; approval document does not specify the expedited review category used to justify the review)[17]
- University of Colorado (initially approved on August 18, 2015, under expedited review categories 5 and 7); of note, the initial IRB approval date is later than the start of the iCOMPARE trial[18]
- The Cooper Health System (initially approved on December 24, 2014, under expedited review categories 5 and 7)[19]
- West Virginia University (initially approved on May 29, 2015, under expedited review category 7)[20]

Under HHS regulations at 45 C.F.R. §46.110, in order to qualify for an expedited IRB review procedure at the time of initial review, research must involve no more than minimal risk and involve *only* procedures that are listed in one or more of seven categories.[21] The iCOMPARE trial fails to qualify for expedited review in both regards.

First, the risks to the first-year resident subjects of being exposed repeatedly to duty shifts significantly longer than the limit of 16 consecutive hours currently mandated by the Accreditation Council for Graduate Medical Education, with reduced time off between scheduled duty shifts,[22] greatly exceeds the threshold for minimal risk, which is defined by the HHS human subjects protection regulations at 45 C.F.R. §46.102(i) as follows:

> *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

As discussed in detail in Public Citizen and AMSA's prior letters to OHRP,[23,24] the resident subjects forced to participate in the iCOMPARE trial are being exposed to increased risks of motor vehicle accidents,[25,26,27] needle-stick and other percutaneous injuries resulting in potential exposure to blood-borne pathogens,[28,29] and depression.[30,31,32]

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[17] *Ibid*. PDF page 24.
[18] *Ibid*. PDF page 26.
[19] *Ibid*. PDF page 29.
[20] *Ibid*. PDF page 39.
[21] 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 March 7, 2016.
[22] Public Citizen and the American Medical Student Association. Letter to the Office for Human Research Protections regarding the iCOMPARE trial. November 19, 2015. http://www.citizen.org/documents/2283.pdf. Accessed March 7, 2016.
[23] *Ibid*.
[24] Public Citizen and the American Medical Student Association. Follow-up letter to the Office for Human Research Protections regarding the iCOMPARE trial. February 11, 2016. http://www.citizen.org/hrg2302. Accessed March 7, 2016.
[25] Barger LK, Cade BE, Ayas NT, et al. Extended work shifts and the risk of motor vehicle crashes among interns. *N Engl J Med*. 2005;352(2):125-134.

Second, the procedures involved in the iCOMPARE trial are not limited to the procedures described in the current list of research categories that may be reviewed under an expedited IRB review procedure, including the following two categories cited by several IRBs that reviewed the iCOMPARE trial under an expedited review procedure:[33]

> Expedited review category 5: Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).
>
> Expedited review category 7: Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

Again, as with the exemption categories discussed above, the scope of the iCOMPARE trial's experimental intervention and other procedures clearly far exceeds the limits of these expedited review categories. The trial does not qualify for IRB review under expedited review category 5 because (a) the intervention being tested at institutions randomized to the experimental group clearly does not constitute research involving materials that have been collected or will be collected solely for nonresearch purposes; and (b) data is being collected from the resident subjects solely for research purposes.

With respect to expedited review category 7, the intervention being tested at institutions randomized to the experimental group and the collection of mortality data on patient subjects clearly is not limited to (a) research on individual or group characteristics or behavior, or (b) research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

Importantly, it is highly doubtful that any single IRB member who reviewed the iCOMPARE trial for each of the IRBs that approved it under an expedited review procedure had sufficient

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[26] Marcus CL, Loughlin GM. Effect of sleep deprivation on driving safety in housestaff. *Sleep*. 1996;19(10):763-766.
[27] Ware JC, Risser MR, Manser T, Karlson KH. Medical resident driving simulator performance following a night on call. *Behav Sleep Med*. 2006;4(1):1-12.
[28] Parks DK, Yetman RJ, McNeese MC, et al. Day-night pattern in accidental exposures to blood-borne pathogens among medical students and residents. *Chronobiol Int*. 2000;17(1):61-70.
[29] Ayas NT, Barger LK, Cade BE, et al. Extended work duration and the risk of self-reported percutaneous injuries in interns. *JAMA*. 2006;296(9):1055-1062.
[30] Sen S, Kranzler HR, Krystal JH, et al. A prospective cohort study investigating factors associated with depression during medical internship. *Arch Gen Psychiatry*. 2010;67(6):557-565.
[31] Berkoff K, Rusin W. Pediatric house staff's psychological response to call duty. *J Dev Behav Pediatr*. 1991;12(1): 6-10.
[32] Gottlieb DJ, Peterson CA, Parenti CM, Lofgren RP. Effects of a night float system on housestaff neuropsychologic function. *J Gen Intern Med*. 1993;8(3):146-148.
[33] 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 March 7, 2016.

breadth of expertise, training, and background to make the complex regulatory and ethical determinations required for IRB approval, including determining: (1) the risks to the resident and patient subjects; (2) whether those risks were minimized by using procedures that are consistent with sound research design; (3) whether those risks are reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge that may reasonably be expected to result; and (4) whether the investigators' proposed plan to not obtain the voluntary informed consent of the resident and patient subjects was ethically and legally permissible.

The inadequacies of these expedited IRB reviews of the iCOMPARE trial were compounded by the fact that the investigators omitted from the iCOMPARE trial protocol and related grant applications critical information regarding the well-documented risks posed to the internal medicine residents who were assigned to the experimental group, as described in detail in Public Citizen and AMSA's February 11, 2016, letter to OHRP.[34]

Uncertain status of IRB review at some institutions

The IRB approval documents for the following institutions did not specify the type of IRB review that occurred:

- Baylor College of Medicine (approved for the period April 7, 2015, until March 10, 2016)[35]
- Lahey Hospital Medical Center (approved on June 5, 2015); importantly, the IRB approval document indicates that the IRB waived the requirement for documenting informed consent with a signed written consent form, but not the requirement for obtaining informed consent[36]
- Mercy Health System (approval letter dated March 9, 2015)[37]
- Texas Tech University Health Sciences Center (the document provided to us is only for an amendment approved under an expedited review procedure on May 7, 2015); importantly, the IRB approval document indicates that the IRB waived the requirement for documenting informed consent with a signed written consent form, but not the requirement for obtaining informed consent[38]

No IRB approval document was provided to us for the Texas A&M College of Medicine-Scott and White program, which was randomized to the experimental group and for which final IRB approval was listed as still pending.

[34] Public Citizen and the American Medical Student Association. Letter to the Office for Human Research Protections regarding the iCOMPARE trial. February 11, 2016. http://www.citizen.org/documents/2302.pdf. Accessed March 7, 2016.
[35] Certification documents for institutional review board review of the iCOMPARE trial. http://www.citizen.org/documents/iCOMPARE-IRB-Certification-docs.pdf. Accessed March 7, 2016. PDF pages 4-5.
[36] *Ibid*. PDF page 17.
[37] *Ibid.* PDF page 19.
[38] *Ibid*. PDF page 25.

Regarding those institutions that waived the requirement for *documenting* informed consent with a signed written consent form, OHRP needs to investigate how the informed consent of both the resident subjects and the patient subjects was obtained for these institutions and whether the process and content of the consent procedures satisfied all requirements of HHS regulations at 45 C.F.R. §46.116. Given the design of the iCOMPARE trial, we cannot conceive of any consent procedure that would have met these regulatory requirements, especially those requiring investigators to "minimize the possibility of coercion or undue influence" and to ensure that "refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled."

Failure to ensure risks to resident subjects are minimized, as required by HHS regulations at 45 C.F.R. §46.111(a)

Public Citizen and AMSA's February 11, 2016, letter to OHRP[39] explained in detail how the design of the iCOMPARE trial — as described in the trial protocol and related grant applications — failed to minimize risks to the resident subjects because, among other reasons, it lacked an appropriate monitoring plan for capturing, on an ongoing basis, all motor vehicle accidents, percutaneous injuries, and episodes of depression experienced by *all* resident subjects — not just the first-year internal medicine residents — in both the experimental and control groups.

Among the records that Public Citizen obtained from NIH were the following:

- A document titled *iCOMPARE Data and Safety Monitoring Plan*, dated October 6, 2015, which was discussed by the NHLBI-established DSMB at its inaugural meeting on October 13, 2015.

- A document titled *iCOMPARE: individualized Comparative Effectiveness Models Optimizing Patient Safety and Resident Education Statistical Analysis Plan, Version 1*, dated October 9, 2015, which also was discussed by the DSMB on October 13, 2015.

- An undated three-page document titled *Process for Identifying Adverse Events Among Resident Physicians in Participating Programs.*

These documents, which appear to have been created more than three months after the iCOMPARE trial began, describe plans for collecting serious adverse events only in first-year internal medicine residents. For example, the October 6, 2015, Data and Safety Monitoring Plan included the following:[40]

[39] Public Citizen and the American Medical Student Association. Letter to the Office for Human Research Protections regarding the iCOMPARE trial. February 11, 2016. http://www.citizen.org/documents/2302.pdf. Accessed March 7, 2016.
[40] iCOMPARE Data and Safety Monitoring Plan. October 6, 2015. http://www.citizen.org/documents/iCOMPARE_Data-Safety-Monitoring-Plan-Oct-6-2015.pdf. Accessed March 7, 2016. PDF pages 1-2.

> In iCOMPARE, the following events will be considered SAEs [serious adverse events]: **death or hospitalization of an intern, removal of an intern from their schedule or rotation because of mental [or] physical condition potentially related to their duty hours, motor vehicle accident in which the intern was the driver, needle stick experienced by intern, and other on the job injury to intern**. [Emphasis added]
>
> NHLBI defines unexpected events as those that are "not consistent with the risk information described in the general investigational plan or elsewhere in the current application". The events considered SAEs in iCOMPARE are not unexpected inside of iCOMPARE but similarly they are not unexpected outside of iCOMPARE. For each SAE listed above, we expect training programs randomized in iCOMPARE to have similar event rates regardless of duty hour schedule assignment.
>
> We will ask each program director to provide a narrative report of occurrence of any of the events listed above. The catchment will be by self-report; program directors will be queried periodically about event occurrence and reminded to provide these reports. The DCC [Data Coordinating Center] will abstract information to provide counts and to calculate rates of occurrence. …
>
> [I]t is impossible to state, a priori, what kind of unanticipated problems we expect in iCOMPARE. However, unanticipated problems in iCOMPARE might include **differential rates across treatment groups of intern fatigue-related accidents, near misses or injuries** … [Emphasis added]

Likewise, the October 9, 2015, Statistical Analysis Plan stated the following:[41]

> **6 Intern safety outcomes**
>
> We will compare the rates of serious adverse events (SAEs) by duty hour group using negative binomial models. The following events will be considered SAEs: death or hospitalization of an intern, removal of an intern from their schedule or rotation because of mental [or] physical condition potentially related to their duty hours, motor vehicle accident in which the intern was the driver, needle stick experienced by intern, and other on the job injury to intern.

Finally, the undated document titled *Process for Identifying Adverse Events Among Resident Physicians in Participating Programs* included the following key excerpts:[42]

> Internal medicine residency programs are typically three years long and so at any one time include residents in their first, second, and third years of training. Under current

[41] iCOMPARE: individualized Comparative Effectiveness Models Optimizing Patient Safety and Resident Education statistical analysis plan, version 1. October 9, 2015. http://www.citizen.org/documents/iCOMPARE_Statistical-Analysis-Plan-Oct-9-2015.pdf. Accessed March 7, 2016. PDF page 9.

[42] Process for identifying adverse events among resident physicians in participating programs. http://www.citizen.org/documents/iCOMPARE-Date-Safety-Monitoring-Plan-Residents.pdf. Access March 7, 2016.

duty hour rules, second and third year internal medicine residents are already permitted to work shifts of up to 28 hours in length. First year residents under current rules established in 2011 typically work shifts no longer than 16 hours, although in their second and third years they will work shift lengths of up to 28 hours. Therefore, the intervention of the iCOMPARE trial effectively allows first year residents to work shift lengths that they could work in their second and third year. Safety monitoring of residents in iCOMPARE is only for interns (residents in their first year) because the flexibility introduced by the iCOMPARE intervention predominantly changes rules affecting first-year residents.

Surveillance of work-related problems in internal medicine residency programs under normal circumstances falls to the directors of those residency programs and it is those usual mechanisms that are employed in the iCOMPARE trial. All program directors, regardless of the assignment of their program to intervention or control, are periodically reminded to report any adverse events through a number of mechanisms, including as part of regular emails and discussion at meetings. **The most recent reminder was sent on December 1, 2015, and reads as follows**: … [Emphasis added]

> From: Kelsey Gangemi [mailto:kgangemi@mail.med.upenn.edu]
> Sent: Tuesday, December 01, 2015 10:25 AM
> To: XXX
> Cc: Asch, David; 'Sanjay Desai'; Judy Shea
> Subject:iCOMPARE Adverse Event Reporting Reminder
>
> Dear iCOMPARE PDs [Program Directors],
>
> As a reminder, it [is] extremely important for you to alert the iCOMPARE study team **as soon as possible** if an adverse event or unanticipated problem occurs with an intern in your program. **It is critical that *both* FLEX and CURR programs report the specified events-this will enable us to accurately compare event rates between groups.** [Emphasis in the original]
>
> For the purposes of this trial, we ask that you report to us the following serious adverse events and unanticipated problems:
>
> - Serious adverse events
> - Death or hospitalization of an intern
> - Removal of an intern from their schedule or rotation because of a mental or physical condition potentially related to their duty hours
> - Motor vehicle accident when the intern was the driver
> - Needle stick experienced by intern

- Unanticipated problems
    - Any unexpected event you assess as being related to participation in the trial that places an intern at greater risk of harm than expected

When reporting an event, please provide the following information:

- Event date
- Descriptive narrative detailing the event, including the kind of rotation the interns were on at the time. …

Reports will be reviewed by numerous study related entities including the trial Directors, the iCOMPARE Data and Safety Monitoring Board and the iCOMPARE Steering Committee.
As a reminder, this is an essential component of the trial and we will prompt for this information regularly to ensure the safety of our trainees.

Please let us know now if you have experienced any events above since July 1st. [Emphasis in the original]

Many thanks,
The iCOMPARE team

* * * * *

In considering the above monitoring plan for resident subjects described in the above documents, it is important to understand that even a perfectly designed plan to collect and monitor serious adverse outcomes in the resident subjects would not be sufficient to make the iCOMPARE trial ethical and compliant with HHS regulations for the protection of human subjects.

Nevertheless, this monitoring plan raises several important points, concerns, and questions that should be evaluated by OHRP:

(1) The creation of the plan to collect, and to have a DSMB monitor, serious adverse events in first-year resident subjects of the iCOMPARE trial unequivocally signals a recognition by the investigators (and, as discussed below, the NHLBI-established DSMB) that the trial's experimental intervention could be exposing the resident subjects to increased risks of motor vehicle accidents, needle-stick and other percutaneous injuries resulting in potential exposure to blood-borne pathogens, and depression due to sleep deprivation. This further supports Public Citizen and AMSA's previously stated contention that the research involves greater than minimal risk for the resident subjects enrolled at institutions randomized to the experimental group.

(2) The statement in the Data and Safety Monitoring Plan that "For each SAE listed above, we expect training programs randomized in iCOMPARE to have similar event rates regardless of duty hour schedule assignment" is troubling because it inappropriately downplays the risks to the resident subjects assigned to the experimental group, thereby

trivializing the known adverse health impact of increased consecutive work hours. Moreover, it reflects — disturbingly — either a lack of awareness of or a deliberate disregard for the substantial body of published evidence showing increased risks of motor vehicle accidents,[43,44,45] needle-stick and other percutaneous injuries resulting in potential exposure to blood-borne pathogens,[46,47] and depression[48,49,50] for residents working long work shifts.

(3) By limiting its scope to interns, the plan misleadingly implies that the experimental intervention involves no risks to second- and third-year residents. While it is true that, as explained above, the iCOMPARE trial disproportionately endangers first-year residents, the experimental intervention also removes the currently mandated 28-hour cap on work-shift duration and the eight-hour minimum time off between shifts for second- and third-year residents and, thus, could increase the work hours of these residents, potentially exposing them to increased risks of fatigue-related adverse events.

(4) Significantly, the details of this monitoring plan were not described in the iCOMPARE trial protocol,[51] related grant applications,[52]or the publicly accessible iCOMPARE trial website.[53] As previously noted, the Data and Safety Monitoring Plan and related documents that were presented to the DSMB appear to have been created more than three months after the iCOMPARE trial began. Therefore, in its investigation of this matter, OHRP needs to seek answers to the following key questions:

(a) When was this plan to monitor serious adverse events in resident subjects created? Was it fully implemented at the start of the trial?

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[43] Barger LK, Cade BE, Ayas NT, et al. Extended work shifts and the risk of motor vehicle crashes among interns. *N Engl J Med*. 2005;352(2):125-134.
[44] Marcus CL, Loughlin GM. Effect of sleep deprivation on driving safety in housestaff. *Sleep*. 1996;19(10):763-766.
[45] Ware JC, Risser MR, Manser T, Karlson KH. Medical resident driving simulator performance following a night on call. *Behav Sleep Med*. 2006;4(1):1-12.
[46] Parks DK, Yetman RJ, McNeese MC, et al. Day-night pattern in accidental exposures to blood-borne pathogens among medical students and residents. *Chronobiol Int*. 2000;17(1):61-70.
[47] Ayas NT, Barger LK, Cade BE, et al. Extended work duration and the risk of self-reported percutaneous injuries in interns. *JAMA*. 2006;296(9):1055-1062.
[48] Sen S, Kranzler HR, Krystal JH, et al. A prospective cohort study investigating factors associated with depression during medical internship. *Arch Gen Psychiatry*. 2010;67(6):557-565.
[49] Berkoff K, Rusin W. Pediatric house staff's psychological response to call duty. *J Dev Behav Pediatr*. 1991;12(1):6-10.
[50] Gottlieb DJ, Peterson CA, Parenti CM, Lofgren RP. Effects of a night float system on housestaff neuropsychologic function. *J Gen Intern Med*. 1993;8(3):146-148.
[51] Individualized Comparative Effectiveness of Models Optimizing Patient Safety and Resident Education (iCOMPARE): Protocol, Version 1.3. October 6, 2015. http://www.citizen.org/documents/iCompare-Protocol.pdf. Accessed March 7, 2016.
[52] University of Pennsylvania grant application for grant number 1U01HL 125388-01A1. http://www.citizen.org/documents/iCOMPARE-grant_1U01HL12538801A1_UPenn_Key Sections.pdf. Accessed March 7, 2016.
[53] iCOMPARE: Comparative Effectiveness of Models Optimizing Patient Safety and Resident Education. http://www.jhcct.org/icompare/. Accessed March 7, 2016.

(b) Was this plan ever submitted to the IRBs that reviewed and approved the trial, and if so, when was it submitted? Has OHRP obtained documents demonstrating those submissions?

We note that inclusion of an appropriately worded plan — one that described the known risks of motor vehicle accidents, needle stick and other percutaneous injuries, and depression — in materials submitted to the IRBs might have alerted them to the serious risks posed by the research to the resident subjects. Without this information, the IRBs that reviewed and approved the iCOMPARE trial — whether under an expedited review procedure or at a convened meeting of the IRB — lacked the information necessary to evaluate the risks of the research to the resident subjects and to determine whether those risks were minimized.

(c) If this plan was not part of the initial protocol reviewed and approved by the IRBs, did the investigators obtain approval of this change to the research from the IRBs, as required by HHS regulations at 45 C.F.R. §46.103(b)(4)?

(d) When were the program directors at all internal medicine training programs participating in the study first instructed to report the following, investigator-defined SAEs: "death or hospitalization of an intern, removal of an intern from their schedule or rotation because of a mental or physical condition potentially related to their duty hours, motor vehicle accident when the intern was the driver, needle stick experienced by intern, and other on the job injury to intern"?[54]

The December 1, 2015, email to program directors presented above is characterized as a "reminder." However, the instruction to "**Please let us know now if you have experienced any events above since July 1st**" [emphasis in the original] raises questions about when such instructions were first delivered to the program directors.

(5) Although the monitoring plan includes some elements of the type of monitoring that would be needed to minimize risks to the resident subjects, as noted in Public Citizen and AMSA's February 11, 2016, letter to OHRP,[55] it is deficient in several regards. For example, the plan:

(a) Excludes adverse event reporting for resident subjects above the first-year training level.

(b) Fails to adequately address the reporting of adverse events for non-internal medicine first-year residents who rotate on internal medicine wards.

[54] Process for identifying adverse events among resident physicians in participating programs. http://www.citizen.org/documents/iCOMPARE-Date-Safety-Monitoring-Plan-Residents.pdf. Access March 7, 2016. PDF page 1.

[55] Public Citizen and the American Medical Student Association. Letter to the Office for Human Research Protections regarding the iCOMPARE trial. February 11, 2016. http://www.citizen.org/documents/2302.pdf. Accessed March 7, 2016.

(c) Lacks critically important instructions for prompting residents themselves to report all types of serious adverse events that might otherwise escape detection by the program directors.

(d) Does not require reporting of any removal of a resident from their schedule or rotation because of a mental or physical condition, regardless of whether it is perceived by the program director to be related to their duty hours.

(e) Does not require monitoring for depression that might not result in removal of a resident from their schedule or rotation.

Records from the DSMB established to monitor the iCOMPARE trial indicate that the board held its inaugural meeting on October 13, 2015, more than three months after the trial began.[56] At that meeting, the DSMB members reviewed and discussed for the first time the DSMB charter, the iCOMPARE trial protocol, the trial's Data and Safety Monitoring Plan, and the Statistical Analysis Plan.

Importantly, the DSMB requested the following at its initial meeting:[57]

> The Data and Safety Monitoring Plan (DSMP) should be modified so that **a resident death is reported within 24 hours of iCOMPARE investigators' awareness of the event**. The DSMP should clarify that the Chair, Dr. [Lia] Logio, who agreed to serve as Medical Officer for the DSMB, and the NHLBI Executive Secretary will receive events that are reported in an expedited manner. [Emphasis added]

The revised Data and Safety Monitoring Plan was to be submitted to the DSMB within one month, which would have been more than four months after the trial began. The failures to have a DSMB established and fully functioning and to finalize the Data and Safety Monitoring Plan *prior* to the initiation of the trial represent additional factors contributing to the failure to ensure that risks to the iCOMPARE subjects are minimized by using procedures consistent with sound research design.

Finally, the DSMB safety monitoring of adverse events in resident subjects — including potential deaths, which could result from motor vehicle accidents or depression-related suicide attempts due to sleep deprivation from exposure to work shifts of 28 or more hours — indicates that the DSMB members recognized that the trial's experimental intervention could be exposing the resident subjects to potentially life-threatening harms. This again confirms Public Citizen and AMSA's previously stated contention that the research involves greater than minimal risk for the resident subjects enrolled at institutions randomized to the experimental group.

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[56] Individualized Comparative Effectiveness of Models Optimizing Patient Safety and Resident Education (iCOMPARE) Data and Safety Monitoring Board (DSMB) teleconference minutes. October 13, 2015. http://www.citizen.org/documents/iCOMPARE-DSMB-Meeting-minutes-10-13-2015_Searchable.pdf. Accessed March 7, 2016.

[57] *Ibid*. PDF page 3.

Conclusions

Each successive disclosure of information regarding the iCOMPARE trial has provided further overwhelming evidence of egregious ethical and regulatory lapses regarding the design, conduct, and IRB oversight of the trial. The trial, as designed and conducted, clearly fails to minimize risks to both the resident and patient subjects and violates ethical and regulatory requirements related to informed consent.

Moreover, the review and oversight of the iCOMPARE trial, as well as the similarly designed Flexibility in Duty Hour Requirements for Surgical Trainees (FIRST) trial, epitomize a human subjects protection system that has failed dismally at all levels, including those of:

- The investigators, who failed to provide the IRBs (or institutional officials who were gatekeepers for the IRBs) with sufficient information about the risks of the experimental intervention and plans for monitoring these risks.
- The IRBs, which inappropriately determined the trials were not human subjects research, qualified for exemption from the human subjects protection regulations, or were eligible for expedited review, and which lacked sufficient expertise and background to adequately evaluate the research and make the ethical and regulatory determinations required for approval.
- NIH, a major funder of the trial, which apparently failed to question IRB certification documents that revealed irreconcilable disparities in the determinations by different IRBs and other institutional officials regarding the status of the iCOMPARE trial, and which allowed the trial to begin before a DSMB was established and fully functioning.
- The DSMB for the iCOMPARE trial, which apparently failed to question why the trial had begun without the DSMB already being established and fully functioning and without the Data and Safety Monitoring Plan having been vetted by the DSMB; and which allowed the trial to proceed without a plan that would allow monitoring of the safety of patient subjects while the trial is ongoing.
- OHRP, which was alerted to the serious ethical and regulatory lapses regarding the iCOMPARE and FIRST trials more than three months ago, but has yet to take meaningful action to intervene to protect human subjects. Because of OHRP's inaction, resident and unwitting patient subjects continue to be forced to participate in greater-than-minimal-risk research without their voluntary informed consent.

We are aware that OHRP's current policy titled *Compliance Oversight Procedures for Evaluating Institutions*[58] indicates that OHRP has discretion regarding whether to initiate a for-cause compliance oversight evaluation of substantive written allegations or indications of non-compliance with the HHS regulations for the protection of human subjects. However, in light of the increasingly overwhelming evidence of widespread, serious ethical and regulatory violations related to the iCOMPARE trial, which is being funded in part by NHLBI, a decision by OHRP to not initiate a formal for-cause compliance oversight evaluation of all institutions participating in

[58] Office for Human Research Protections. Compliance oversight procedures for evaluating institutions. October 14, 2009. http://www.hhs.gov/ohrp/compliance/evaluation/index.html. Accessed March 7, 2016.

this unethical trial would constitute an unacceptable abuse of the agency's discretion and an abrogation of its fundamental responsibility to protect human subjects.

In a separate letter to Acting Assistant Secretary Dr. Karen DeSalvo, we are requesting an urgent meeting with her and you to discuss this untenable situation.

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

Sincerely,

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cc: The Honorable Sylvia Mathews Burwell, Secretary of Health and Human Services
The Honorable Karen B. DeSalvo, Acting Assistant Secretary for Health