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February 11, 2016

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Re: Individualized Comparative Effectiveness of Models Optimizing Patient Safety and Resident Education (iCOMPARE) Trial
Sponsor: National Heart, Lung and Blood Institute
Award Numbers: 1U01HL 125388-01A1 (Principal Investigator: David A. Asch, University of Pennsylvania); 1U01HL 126088-01A1 (Principal Investigator: James A. Tonascia, Johns Hopkins University)
ClinicalTrials.gov Identifier: NCT02274818

Dear Drs. Menikoff and Borror:

Public Citizen and the American Medical Student Association are writing in follow-up to our November 19, 2015, letter urging the Office for Human Research Protections (OHRP) to 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.

Since November 19, we have obtained from the National Institutes of Health (NIH), under a Freedom of Information Act request, copies of the iCOMPARE trial protocol and the related NIH grant applications. Our review of these documents provides additional clear evidence that the iCOMPARE trial, as designed and currently being conducted, violates basic ethical principles and federal regulatory requirements related to the protection of human subjects. These violations include failures to minimize risks to the subjects and to obtain their voluntary informed consent.

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

Investigators provided insufficient information about risks to resident subjects

Our review of the iCOMPARE trial protocol and related grant applications reveals that the investigators withheld from these documents critical information regarding the well-known risks posed to the internal medicine residents who were assigned to the experimental group. As a result, the institutional review boards (IRBs) that reviewed and approved the iCOMPARE trial lacked the information necessary to evaluate the risks of the research to the resident subjects and to determine whether those risks were minimized.

Strikingly absent from the iCOMPARE trial protocol[1] — presumably the key document reviewed by the IRBs — is any discussion of the known significant risks of excessively long work shifts and the resulting sleep deprivation in medical residents. As discussed in detail in our November 19 letter, these include increased risks of motor vehicle accidents,[2,3,4] needle-stick and other percutaneous injuries resulting in potential exposure to blood-borne pathogens,[5,6] and depression.[7,8,9]

Section 13.2.4 of the protocol — "Consent for end of year and just in time survey data" — briefly mentions that the resident subjects will complete surveys that query "their attitudes and **burnout** at the end of the intervention year" [emphasis added].[10] Section 13.3.4 — "Intern sleep and alertness" — also states that "To mitigate **risks of fatigue**, all trainees will be required to receive structured education in **sleep deprivation and fatigue** management in June 2015" [emphasis added].[11] These statements hint at the risks of the research for the resident subjects, but fail to provide any meaningful discussion of the these risks.

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[1] Individualized Comparative Effectiveness of Models Optimizing Patient Safety and Resident Education (iCOMPARE): Protocol, Version 1.3. October 6, 2015. http://www.hhs.gov/ohrp/compliance/evaluation/index.html. Accessed February 10, 2016.
[2] 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. Survey response rate: 80% of interns who volunteered to participate.
[3] Marcus CL, Loughlin GM. Effect of sleep deprivation on driving safety in housestaff. *Sleep*. 1996;19(10):763-766. Survey response rate: 87% of residents.
[4] 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.
[5] 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.
[6] 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.
[7] 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.
[8] Berkoff K, Rusin W. Pediatric house staff's psychological response to call duty. *J Dev Behav Pediatr*. 1991;12(1):6-10.
[9] 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.
[10] 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 February 10, 2016. PDF page 35.
[11] *Ibid*. PDF page 36.

The grant applications do include several cursory, nonspecific references to information that might have alerted the IRBs to the known risks that the experimental intervention would pose to resident subjects — assuming the IRBs received and reviewed these applications. For example, the grant application submitted to the NIH by the University of Pennsylvania (principal investigator David A. Asch) provided the following pertinent information in discussing the background, rationale, and potential risks for the trial:

- "Since 2003, resident physician duty hours have been regulated across the US in the interest of reducing **resident fatigue** and promoting patient safety."[12] [emphasis added]
- "*Trainees in [the experimental group] will report greater satisfaction with their educational experience (greater ownership, greater continuity and **lower burnout**) than trainees in [the control group]*."[13] [italics in original, bold emphasis added]
- "United States policy limiting work hours in graduate medical education has become central to a highly charged debate surrounding the safety of patients cared for by resident physicians, the **safety of resident physicians** …"[14] [emphasis added]
- "The 2009 IOM report identified the need to balance **fatigue mitigation** with continuity and education …"[15] [emphasis added]
- "The implementation of recent duty hour standards was intended to reduce **resident fatigue** and thereby increase **resident** and patient **safety**, but these rules have raised their own safety concerns associated with fragmented continuity, as well as educational concerns for the trainees who will become our independent physicians of the future."[16] [emphasis added]
- "In the years since the implementation of the 2003 duty hours standards, a number of studies documented trainees' and program directors' reactions and perceptions to education, clinical care, and **well-being**. Views are mixed. Multiple studies report **reduced burnout** post 2003 duty hour reform, and **improved quality of life**, while other studies report **burnout in the majority of residents**, whether sampled after the 2003 or the 2011 policy changes."[17] [emphasis added]

(See also the grant excerpts in the next section below.)

As with the information in the iCOMPARE trial protocol, the information discussed by the investigators in their grant applications lacks any meaningful discussion of the actual risks to the resident subjects and, therefore, was insufficient for the IRBs to assess these risks and determine whether they were minimized.

[12] University of Pennsylvania grant application for grant number 1U01HL 125388-01A1. http://www.citizen.org/documents/iCOMPARE-grant_1U01HL12538801A1_UPenn_Key Sections.pdf. Accessed February 10, 2016. PDF page 17.
[13] *Ibid*. PDF page 17.
[14] *Ibid*. PDF page 18.
[15] *Ibid*. PDF page 18.
[16] *Ibid*. PDF page 20.
[17] *Ibid*. PDF page 24.

Even more troubling is the fact that the references provided in the "Literature Cited" section of the University of Pennsylvania grant application[18] included citations of key studies regarding risks of motor vehicle accidents[19] and needle-stick and other percutaneous injuries[20] in first-year residents, but we find no discussion of these studies in the body of the grant application. Moreover, in the discussion of the trial's potential risks in the Protection of Human Subjects section of the grant application, the investigators made the statement:"**The greatest risk to participants is the risk to confidentiality**" [emphasis added].[21]

The withholding of information about the actual known risks of the trial for the resident subjects, combined with the inclusion of the statement that the greatest risk to subjects was a possible breach of confidentiality, undoubtedly misled the IRBs that reviewed and approved the trial.

Unsound research design resulted in a failure to minimize risks to the resident subjects

HHS regulations at 45 C.F.R. 46.116(a)(1) require that risks to subjects by minimized by using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk. One important component of a sound research design for a clinical trial such as iCOMPARE is a robust plan to continuously and actively monitor subjects for important adverse outcomes that have been identified as risks of the research. The iCOMPARE trial investigators failed to include in their trial design clearly defined, robust procedures for continuous active monitoring of resident subjects for motor vehicle accidents, percutaneous injuries, and depression.

With respect to monitoring adverse health outcomes in the resident subjects, the investigators described only the following procedures in the protocol and grant application:

Protocol:

- "**9.3.2. Trainee end of year surveys:** Trainees will be surveyed twice, in May 2015 and May 2016. … The surveys will query perceptions and satisfaction with work and supervision."[22] [bolding in original]
- "**9.3.3 Trainee just in time surveys:** These surveys will be administered throughout the intervention year and will be directed to a random sample of the interns in target [internal medicine] rotations. … The surveys will query training experiences in the prior 24 hours

[18] *Ibid*. PDF page 40.
[19] 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. Survey response rate: 80% of interns who volunteered to participate.
[20] 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.
[21] University of Pennsylvania grant application for grant number 1U01HL 125388-01A1. http://www.citizen.org/documents/iCOMPARE-grant_1U01HL12538801A1_UPenn_Key Sections.pdf. Accessed February 10, 2016. PDF page 32.
[22] 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 February 10, 2016. PDF page 23.

– e.g., number and types of patient encounters and participation in education activities."[23] [bolding in original]

Grant application (1U01HL125388-01A1):

- "*Group 2 trainees* will participate in iCOMPARE from June 2015 through June 2016. … These trainees will be asked to complete assessments querying their attitudes, burnout, and mood/empathy at the end of the intervention year."[24] [italics in original]
- "We will use the Maslach Burnout Inventory, a 22-item rating scale designed to assess three aspects of the burnout syndrome: emotional exhaustion (9 items), depersonalization (5 items), and lack of personal accomplishment (8 items) [to be administered in June 2016]."[25]
- "Internal monitoring of data and safety. The Steering Committee will monitor accumulating safety and performance data at regularly scheduled intervals to help assure participant safety and for quality assurance. … As data collection begins, the Steering Committee will begin to monitor progress of … reports of safety concerns for trainees, faculty or patients that are possibly or definitely related to iCOMPARE."[26] [underlining in original]
- DSMB [Data and Safety Monitoring Board] monitoring of safety and performance data. … Once the trial starts, the DSMB will monitor the accumulating performance data to ensure trainee safety and to review education and sleep outcomes acquisition and quality. … [I]ntern survey data on alertness, fatigue-related accidents, near misses, work intensity, mood, and time-motion, and trainee and faculty survey data on satisfaction will be accumulating on a continuous basis during the trial and will be included in each DSMB report as available."[27] [underlining in original]

The above limited surveys of the resident subjects are seriously deficient in three key respects. First, in terms of scope of information collected, although the grant application refers to DSMB monitoring of intern survey data on fatigue-related accidents, near misses, and mood, there is no plan described in either the protocol or grant applications for systematically collecting accurate information on motor vehicle accidents, percutaneous injuries, and depression. Second, in terms of the subject population, only internal medicine residents are being surveyed,[28] not residents from other specialties who are required to rotate on internal medicine services at experimental group programs, thus exposing them to the same risks of the trial. Also, the just-in-time surveys only go to a subset of internal medicine interns each time and, in addition, are not being administered to any second- or third-year internal medicine residents. Third, in terms of timing, the Maslach Burnout Inventory is to be administered only once, at the *end* of the intervention year in June 2016.

[23] *Ibid*. PDF page 23.
[24] University of Pennsylvania grant application for grant number 1U01HL 125388-01A1. http://www.citizen.org/documents/iCOMPARE-grant_1U01HL12538801A1_UPenn_Key Sections.pdf. Accessed February 10, 2016. PDF page 30.
[25] *Ibid*. PDF page 26.
[26] *Ibid*. PDF page 34.
[27] *Ibid*. PDF page 34.
[28] *Ibid.* PDF page 30.

An appropriate monitoring plan would include detailed procedures for capturing, on an ongoing basis, all motor vehicle accidents and percutaneous injuries experienced by *all* resident subjects — not just the internal medicine residents and not just interns — in both the experimental and control groups. Reports of such events should be actively solicited and monitored on an ongoing basis, regardless of whether the events are considered possibly or definitely related to participation in the iCOMPARE trial (in a randomized trial, such [otherwise subjective] causal determinations are possible only after comparing the number of *all* such events in each group). Frequent (e.g., weekly) reminders and a Web-based portal for residents, program directors, and occupational health clinics to submit reports of all such events would facilitate effective monitoring of such events. Likewise, all resident subjects should be screened periodically throughout the trial for symptoms of depression, including suicidal ideation.

A second important component of a sound research design for a clinical trial such as iCOMPARE is a robust plan for mitigating risks to the subjects. Once again, the trial design as described in both the iCOMPARE trial protocol and grant applications lacks a meaningful plan for accomplishing this for the resident subjects.

With respect to mitigating risks in the resident subjects, the investigator described only the following procedures in the protocol and grant applications:

Protocol:

- "**13.3.4. Intern sleep and alertness:** To mitigate risks of fatigue, all trainees will be required to receive structured education in sleep deprivation and fatigue management in June 2015."[29] [bolding in original]

Grant application (1U01HL125388-01A1):

- "Safety. Both acute and chronic sleep loss, as well as night duty, occur in all trainee schedules including [the control and experimental schedules]. Therefore, for safety, fatigue management strategies (e.g., increased sleep when possible, effective use of caffeine, reduced exposure to light when sleeping, and increased exposure when awake) will be provided to all enrollees in the trial to help protect against fatigue-related risks."[30] [underlining in original]
- "*Fatigue management:* … Since both [the experimental and control] schedules involve night work and some sleep loss, the trial will also include fatigue risk management training (FRMT) for interns to mitigate fatigue risks inherent in both schedules, prior to beginning their internships. To mitigate risks of fatigue, all interns will receive structured education in sleep deprivation and fatigue management in June 2015. FRMT will be made available to all interns in the participating IM program, and focuses on the use of

[29] 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 February 10, 2016. PDF page 36.
[30] University of Pennsylvania grant application for grant number 1U01HL 125388-01A1. http://www.citizen.org/documents/iCOMPARE-grant_1U01HL12538801A1_UPenn_Key Sections.pdf. Accessed February 10, 2016. PDF page 29.

> scientifically-based fatigue countermeasures in three areas: (1) the use of **prophylactic napping to reduce fatigue risk** when working at night, and to extend recovery sleep time after a work period; (2) the use of caffeine, bright light, and face-washing to mitigate the **adverse cognitive effects of sleep inertia** after any sleep period; and (3) ways to prevent, identify and counter **driving drowsy when transiting to/from work**. FRMT will be delivered via a web-based e-learning module developed by Pulsar Informatics, and will include assessment questions to ascertain whether the material is understood. Each intern at each participating program will complete the FRMT module before starting their training and results will be available to the Program Directors."[31] [italics and underlining in original, bolding emphasis added]

It is doubtful that completion of a single Web-based module about fatigue risk management will be effective. This likely is one of dozens of such trainings that these interns undergo prior to the start of their internships. Moreover, the investigators offer no evidence that the Web-based module about fatigue risk management has any effectiveness in mitigating risks of motor vehicle accidents, percutaneous injuries, and depression in residents. Finally, it is our understanding that neither residents from other specialties who are required to rotate on internal medicine services nor second- and third-year internal medicine residents at programs participating in the iCOMPARE trial were required to complete the Web-based module at the beginning of the trial.

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

Just as they failed to include adequate plans for monitoring harms in resident subjects, the investigators also failed to include in their trial design adequate plans for monitoring the safety of the patient subjects.

In particular, given that (a) available evidence indicates that sleep deprivation from excessively long work shifts can increase the rate of serious medical errors by interns;[32] (b) the primary outcome being measured in the trial is 30-day patient mortality;[33] and (c) key secondary endpoints include patient complication rates, 7-day and 30-day readmission rates, and the rate of prolongation of hospital stays,[34] the investigators should have ensured that the trial design included a robust plan for DSMB monitoring of these primary and secondary safety outcomes during the course of the trial. However, the iCOMPARE trial protocol explicitly states that because the patient safety data to be collected (mortality, complications, readmissions, and length of hospital stays) are to be obtained solely from Medicare datasets that will not be available until after the trial intervention is over, "**the DSMB will not review any interim patient safety … outcomes**" [emphasis added].[35]

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[31] *Ibid*. PDF page 33.
[32] Landrigan CP, Rothschild CM, Cronin JW, et al. Effect of reducing interns' work hours on serious medical errors in intensive care units. *N Engl J Med. 2004;*351(18): 1838-1848.
[33] 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 February 10, 2016. PDF pages 11-12.
[34] *Ibid.* PDF page 11.
[35] *Ibid*. PDF page 33.

The failure to have a DSMB monitor such critically important safety outcomes in a randomized clinical trial that is likely to involve hundreds of thousands of patient subjects — half of whom will be exposed to an experimental intervention with known risks — renders impossible the basic monitoring function of the DSMB. As a result, the design of the iCOMPARE trial is unsound and fails to minimize risk to the patient subjects.

Inappropriate use of the waiver of informed consent requirements permitted under 45 CFR 46.116(c)

In our November 19 letter, we asked OHRP to investigate the iCOMPARE trial investigators' failure to obtain and document the informed consent of the resident subjects and patient subjects who are enrolled in the trial. When writing our prior letter, we had assumed that the University of Pennsylvania's IRB — the designated lead IRB that reviewed and approved the iCOMPARE trial — had relied upon the waiver of informed consent permitted under HHS regulations at 45 C.F.R. 46.116(d) and had incorrectly found that the trial involves no more than "minimal" risk to the subjects. However, based upon our review of the iCOMPARE trial protocol, we now realize that the IRB relied instead upon the waiver provisions under HHS regulations at 45 C.F.R. 46.116(c). In particular, we note the following statement in the protocol:

- "The Penn IRB has granted iCOMPARE waiver of the requirement to obtain informed consent from trainees and faculty for these data under HHS regulations at 45 CFR 46.116(c). The Penn IRB recognized that iCOMPARE could not practicably be carried out without the waiver and is designed to study, evaluate, or otherwise examine possible changes in or alternatives to current standards for graduate medical education. Thus iCOMPARE meets the criteria for waiver of consent." [36] [underlining in original]
- "The Penn IRB has granted iCOMPARE waiver of the requirement to obtain informed consent from patients for these data under HHS regulations at 45 CFR 46.116(c). The Penn IRB recognized that iCOMPARE could not practicably be carried out without the waiver and is designed to study, evaluate, or otherwise examine possible changes in or alternatives to current standards for graduate medical education. Thus iCOMPARE meets the criteria for waiver of consent." [37] [underlining in original]

The provisions for waiver of informed consent under HHS regulations at 45 C.F.R. 46.116(c) are as follows:

> An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:
>
> (1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or

[36] *Ibid*. PDF page 34.
[37] *Ibid*. PDF page 35.

alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and
(2) The research could not practicably be carried out without the waiver or alteration.

The decision by University of Pennsylvania's IRB to waive informed consent for the iCOMPARE trial subjects under the 45 C.F.R. 46.116(c) was clearly inappropriate because the research does not satisfy the first criterion under the waiver. First, the trial is not being conducted by or subject to the approval of any state or local government officials. Second, the research is not studying, evaluating, or examining a public benefit or service program, but instead is studying the effects of different work hour schedules for internal medicine residents on health outcomes in both patients and the residents.

Importantly, by relying on the provisions of HHS regulations under 45 C.F.R. 46.116(c) to grant the waiver of informed consent for the trial, the IRB was able to avoid making a determination about the level of risk posed by the research to both the resident and patient subjects. Had the IRB waived informed consent under the requirements of 45 C.F.R. 46.116(d), it would have had to find and document that the research involved no more than minimal risk to the subjects.

Conclusions

The additional information gleaned from our review of the iCOMPARE trial protocol and grant applications provides further evidence of egregious ethical and regulatory violations regarding the design, conduct, and IRB review of the trial. The trial as designed clearly fails to minimize risk to both the resident and patient subjects and violates ethical and regulatory requirements related to informed consent.

We renew our call for OHRP to immediately take the following actions:

(1) Invoke its authority under the OHRP-approved Federalwide Assurance (FWA)[38] for each institution engaged in the iCOMPARE trial by suspending the conduct of the trial; and

(2) Launch a compliance oversight investigation into the iCOMPARE trial and appropriately sanction all institutions engaged in the research.

Finally, we are troubled by OHRP's failure so far to take these requested actions. It has now been 12 weeks since our initial complaint letter was submitted to your office. Resident and unwitting patient subjects continue to be forced to participate in greater-than-minimal-risk research without their voluntary informed consent. Your continued inaction makes OHRP a culpable party in this unethical research.

[38] Office for Human Research Protections. Compliance oversight procedures for evaluating institutions. October 14, 2009. http://www.hhs.gov/ohrp/compliance/evaluation/index.html. Accessed February 10, 2016.

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

Sincerely,

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