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November 19, 2015

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1101 Wootton Parkway, Suite 200
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Kristina Borror, Ph.D.
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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: 1U01HL125388-01A1 (Principal Investigator: David A. Asch, University of Pennsylvania); 1U01HL126088-01A1 (Principal Investigator: James A. Tonascia, Johns Hopkins University)
ClinicalTrials.gov Identifier: NCT02274818

Dear Drs. Menikoff and Borror:

Public Citizen, a consumer advocacy organization with more than 400,000 members and supporters nationwide, and the American Medical Student Association, representing more than 40,000 physicians in training, strongly urge the Office for Human Research Protections (OHRP) to immediately suspend the NIH-funded iCOMPARE clinical trial, launch a compliance oversight investigation of the research, and appropriately sanction all institutions engaged in it. The trial, as designed and conducted, 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.

The most egregious ethical and regulatory violations are as follows:

(1) Under the iCOMPARE trial protocol, first year (PGY-1) internal medicine residents at 63 internal medicine residency training programs across the U.S. (see Appendix) and their affiliated hospitals have been randomly assigned to one of the following two

interventions in their work treating patients at hospitals affiliated with these training programs:

(a) A "usual care" duty-hour schedule that complies with the current requirements of the Accreditation Council for Graduate Medical Education (ACGME), which includes a duty-shift cap of 16 consecutive hours (control group); or

(b) A less restrictive flexible duty-hour schedule that allows duty shifts of unlimited duration; these shifts could reach 30 consecutive hours or more, a shift duration that has been shown to be harmful to the health and well-being of medical residents, and likely to their patients as well (experimental group).

The trial investigators are knowingly exposing the PGY-1 residents randomized to the experimental group to previously well-documented greater risks of motor vehicle accidents, percutaneous injuries and exposure to blood-borne pathogens, depression, and, possibly, poorer obstetric outcomes. The serious health risks of long medical resident duty-hour shifts were recognized by the Institute of Medicine (IOM) in a 2009 report[1] and were among the reasons for the ACGME's 2011 decision to impose the current restrictions on PGY-1 medical resident duty-hour schedules.[2]

Therefore, the control and experimental groups in the iCOMPARE trial are not in equipoise with respect to the health of the internal medicine resident subjects. For the experimental group subjects, the trial violates the Belmont Report's basic ethical principle of beneficence[3] because the trial intervention unnecessarily exposes them to known, avoidable risks of serious harm which do not outweigh any possible benefits of the research. Likewise, the design and conduct of the trial fails to ensure that (a) the risks to the internal medicine PGY-1 resident subjects in the experimental group are minimized by using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk, as required by HHS human subjects protection regulations at 45 C.F.R. §46.111(a)(1); and (b) the risks to these subjects are reasonable in relation to the anticipated benefits, if any, to the subjects and the importance of the knowledge that may reasonably be expected to result, as required by HHS human subjects protection regulations at 45 C.F.R. §46.111(a)(2).

(2) The investigators failed to obtain and document the informed consent of the internal medicine resident subjects and the patient subjects who are enrolled in this experiment. According to available protocol documents, "[medical residents] participating in

[1] Institute of Medicine. *Resident Duty Hours: Enhancing Sleep, Supervision, and Safety*. Washington, DC: The National Academies Press; 2009. http://www.nap.edu/catalog/12508/resident-duty-hours-enhancing-sleep-supervision-and-safety. Accessed November 17, 2015.
[2] Accreditation Council for Graduate Medical Education. *The ACGME 2011 Duty Hour Standards: Enhancing Quality of Care, Supervision, and Resident Professional Development*. 2011. https://www.acgme.org/acgmeweb/Portals/0/PDFs/jgme-monograph%5B1%5D.pdf. Accessed November 17, 2015.
[3] 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 November 17, 2015.

> iCOMPARE will consent by completing the study surveys."[4] In addition, according to a recent media report, the University of Pennsylvania's institutional review board (IRB) — the designated lead IRB that reviewed and approved the trial — incorrectly found that the trial involves only "minimal" risk and waived the requirements for obtaining informed consent for all subjects.[5]
>
> The failure to obtain the informed consent of the internal medicine resident subjects (and of the patient subjects as well) first and foremost violates the Belmont Report's basic ethical principle of respect for persons.[6] Furthermore, as discussed in (1) above, the experimental group intervention is exposing the internal medicine resident subjects to risks that far exceed minimal risk. Therefore, 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 fails to comply with the requirements of HHS human subjects protection regulations at 45 C.F.R. §46.116(a).

Importantly, it seems highly unlikely that a trial that involves randomizing medical residents to the less restrictive flexible duty-hour schedule with longer shifts and less time off between shifts could ever be designed and conducted in a manner that would satisfy the Belmont Report's basic ethical principles or the HHS human subjects protection regulations.

The following is a more detailed discussion of the iCOMPARE trial, its serious ethical and regulatory failings, and our requested actions.

iCOMPARE trial design[7,8,9]

The iCOMPARE trial used cluster randomization. Sixty-three internal medicine residency training programs were randomly assigned to either the current ACGME-mandated duty-hour schedule (usual care control group) or to a less restrictive flexible duty-hour schedule (experimental group). The currently ongoing experimental trial interventions started on July 1,

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[4] iCOMPARE trial information: Frequently asked questions. September 2014. http://www.jhcct.org/icompare/docs/iCOMPARE%20-%20Frequently%20Asked%20Questions%20%2820140908%29.pdf. Accessed November 17, 2015.

[5] Bernstein L. Some new doctors are working 30-hour shifts at hospitals around the U.S. *The Washington Post*. October 28, 2015. https://www.washingtonpost.com/national/health-science/some-new-doctors-are-working-30-hour-shifts-at-hospitals-around-the-us/2015/10/28/ab7e8948-7b83-11e5-beba-927fd8634498_story.html. Accessed November 17, 2015.

[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 November 17, 2015.

[7] ClinicalTrials.gov. Individualized Comparative Effectiveness of Models Optimizing Patient Safety and Resident Education (iCOMPARE). NCT02274818. https://clinicaltrials.gov/ct2/show/NCT02274818?term=nct02274818&rank=1. Accessed November 1, 2015.

[8] iCOMPARE: Individualized Comparative Effectiveness of Models Optimizing Patient Safety and Resident Education. http://www.jhcct.org/icompare/. Accessed November 17, 2015.

[9] National Institutes of Health. Research portfolio online reporting tools. Project information for 1U01HL125388-01A1. https://projectreporter.nih.gov/project_info_description.cfm?aid=8962869&icde=26807259&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC. Accessed November 17, 2015.

2015, and are scheduled to end on June 30, 2016 — although an ACGME waiver of its 2011 duty-hour standards for all iCOMPARE trial experimental group training programs, which allowed the investigators to conduct the trial, inexplicably remains in effect for an extended time period following the projected end of the one-year randomized experiment. (Several publicly available iCOMPARE documents indicate that the ACGME waiver for the participating internal medicine training programs will continue until June 2019,[10,11,12] although one document indicates that the waiver will end in June 2017.[13])

Control group intervention

For the training programs assigned to the control group intervention, resident duty-hour schedules must comply with all current ACGME duty-hour requirements that were mandated in 2011, including the following limits on maximum duty period length and minimum time off between scheduled duty periods:[14]

- Duty periods for PGY-1 residents must not exceed 16 hours in duration.
- Duty periods for PGY-2 residents and above may be scheduled for a maximum of 24 hours of continuous duty in the hospital. Residents may remain on-site for transition care, but no longer than four hours.
- Residents must not be assigned additional clinical responsibilities after 24 hours of continuous in-house duty.
- PGY-1 residents should have 10 hours, and must have eight hours, free of duty between scheduled duty periods.
- Intermediate-level residents should have 10 hours free of duty, and must have eight hours between scheduled duty periods. They must have at least 14 hours free of duty after 24 hours of in-house duty.

In explaining the rationale for increasing the restrictions on medical resident duty time in 2011 to a maximum of 16 hours for PGY-1 residents, the ACGME noted the following with respect to resident health and well-being:[15]

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[10] iCOMPARE trial information: Executive summary. September 2014. http://www.jhcct.org/icompare/docs/iCOMPARE%20-%20Design%20Summary%20(20140908).pdf. Accessed November 17, 2015.
[11] iCOMPARE trial information: Frequently asked questions. http://www.jhcct.org/icompare/docs/iCOMPARE%20-%20Frequently%20Asked%20Questions%20(20140908).pdf. Accessed November 17, 2015.
[12] iCOMPARE trial information: Eligibility and program selection. September 2014. http://www.jhcct.org/icompare/docs/iCOMPARE%20-%20Eligibility%20and%20Program%20Selection%20(20140908).pdf. Accessed November 17, 2015.
[13] iCOMPARE. Timeline and upcoming activities for enrolled programs. http://www.jhcct.org/icompare/Timeline.asp. Accessed November 17, 2015.
[14] Accreditation Council for Graduate Medical Education. Resident duty hours in the learning and working environment: Comparison of 2003 and 2011 standards. https://www.acgme.org/acgmeweb/Portals/0/PDFs/dh-ComparisonTable2003v2011.pdf. Accessed November 17, 2015.
[15] Accreditation Council for Graduate Medical Education. *The ACGME 2011 Duty Hour Standards: Enhancing Quality of Care, Supervision, and Resident Professional Development*. 2011. https://www.acgme.org/acgmeweb/Portals/0/PDFs/jgme-monograph%5B1%5D.pdf. Accessed November17, 2015.

- Resident well-being and an improved balance between residents' professional and personal lives is one area where the body of literature on the effects of common duty-hour limits has produced relatively unequivocally positive findings.
- An anticipated effect of the 2003 standards was improvement in resident mood and quality of life, which has been borne out by several studies across multiple specialties.

Of note, the IOM's 2009 report, *Resident Duty Hours: Enhancing Sleep, Supervision, and Safety*, recommended that for *all* medical residents, "scheduled continuous duty periods must not exceed 16 hours unless a 5-hour uninterrupted continuous sleep period is provided between 10 p.m. and 8 a.m."[16]

Experimental group intervention

For the training programs assigned to the experimental group intervention, residents are exposed to less restrictive flexible duty-hour schedules. In particular, all of the above-listed ACGME-mandated limits on maximum duty period length and minimum time off between scheduled duty periods have been eliminated, and only three rules apply:[17]

- An 80-hour per week maximum duty limit averaged over a four-week period.
- One day off per week averaged over a four-week period.
- In-house call no more frequent than every three nights, averaged over a four-week period.

Of note, the same experimental intervention was also used in the Flexibility in Duty Hour Requirements for Surgical Trainees trial (the FIRST trial), a nearly identical trial that involved general surgery residency training programs.[18] For the FIRST trial experimental group, the following changes in resident duty-hour schedules were recommended by the research team:[19]

- PGY-1 residents should take 24-hour calls instead of shorter [i.e., 16-hour] shifts.
- Residents should be encouraged to stay post-call as needed (beyond four hours) for a variety of clinical and non-clinical tasks.
- All residents may be scheduled to round following 24-hour call.
- Residents should be encouraged to stay late (with less time between duty shifts than that currently mandated by the ACGME) for a variety of clinical and non-clinical tasks.

While the iCOMPARE trial's experimental group intervention allows for extensions of duty shift duration and decreases in time off between scheduled duty periods for internal medicine

[16] Institute of Medicine. *Resident Duty Hours: Enhancing Sleep, Supervision, and Safety.* Washington, DC: The National Academies Press; 2009. http://www.nap.edu/catalog/12508/resident-duty-hours-enhancing-sleep-supervision-and-safety. Accessed November 17, 2015.
[17] iCOMPARE: Individualized Comparative Effectiveness of Models Optimizing Patient Safety and Resident Education. http://www.jhcct.org/icompare/. Accessed November 17, 2015.
[18] Flexibility in Duty Hour Requirements for Surgical Trainees Trial – "the FIRST trial". Study overview. http://www.thefirsttrial.org/Overview/Overview. Accessed November 17, 2015.
[19] FIRST trial recommendations for intervention arm hospitals. http://www.thefirsttrial.org/Documents/Summary%20of%20Suggested%20Intervention%20Arm%20Changes.pdf. Accessed November 17, 2015.

residents at all training levels (PGY-1 and above) beyond those permitted under current ACGME requirements, it is clear that PGY-1 internal medicine resident subjects are being exposed to the greatest increased risk. Under the trial protocol, the maximum duty shift duration for PGY-1 residents can routinely be increased from the ACGME-mandated maximum of 16 hours to 28 hours or more. Indeed, PGY-1 residents enrolled in the iCOMPARE trial at internal medicine training programs randomized to the experimental group have reported working 30-hour duty shifts, which is nearly double the ACGME-mandated maximum duty period length.[20]

Outcome measures

The primary outcome measure in the iCOMPARE trial is the 30-day patient subject mortality rate.[21]

Secondary outcomes include measures of PGY-1 internal medicine resident subjects' education and average daily sleep.[22]

Importantly, the iCOMPARE trial is designed as a non-inferiority trial.[23] The researchers are seeking to demonstrate that the mortality rate in the experimental group patient subjects will not be higher than that in the control group patient subjects by more than a pre-specified amount (the non-inferiority margin). The null hypothesis being tested is that the patient subject mortality in the experimental group will be higher than that in the control group by a value greater than the non-inferiority margin.

Data for the outcome measures are being obtained from Medicare claims records, surveys periodically administered by the ACGME and the Association of Program Directors in Internal Medicine, American College of Physicians in-training examination scores, and trial-specific beginning and end-of-year surveys of internal medicine resident subjects.[24]

Unacceptable risk for the experimental group internal medicine resident subjects

There is a substantial body of evidence that increasing the duration of duty shifts for medical residents and the resulting sleep deprivation poses significant risks to their health and well-being. Four serious outcomes have been studied extensively: motor vehicle accidents, percutaneous injuries and exposure to blood-borne pathogens, depression, and poor obstetric outcomes.

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[20] Bernstein L. Some new doctors are working 30-hour shifts at hospitals around the U.S. *The Washington Post*. October 28, 2015. https://www.washingtonpost.com/national/health-science/some-new-doctors-are-working-30-hour-shifts-at-hospitals-around-the-us/2015/10/28/ab7e8948-7b83-11e5-beba-927fd8634498_story.html. Accessed November 17, 2015.

[21] National Institutes of Health. Research portfolio online reporting tools. Project information for 1U01HL125388-01A1. https://projectreporter.nih.gov/project_info_description.cfm?aid=8962869&icde=26807259&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC. Accessed November 17, 2015.

[22] *Ibid.*

[23] *Ibid*.

[24] iCOMPARE trial information: Executive summary. September 2014. http://www.jhcct.org/icompare/docs/iCOMPARE%20-%20Design%20Summary%20(20140908).pdf. Accessed November 17, 2015.

Motor vehicle accidents

A1996 study found that 23 percent of pediatric residents at Johns Hopkins Hospital reported falling asleep while driving, with 71 percent of the incidents happening following call shifts averaging 33 hours.[25] Forty-four percent of pediatric residents reported falling asleep while stopped at a traffic light, with all such incidents occurring post-call. One resident reported that she "routinely used her emergency brakes when stopped at a light because of her sleepiness post-call."

In a 2005 *New England Journal of Medicine* study, the Harvard Work Hours, Health, and Safety Group collected monthly data from 2,737 interns across the U.S. to investigate the relationship between hours worked and motor vehicle accidents, near misses, and incidents involving involuntary sleeping while driving.[26] Interns' risk of a motor vehicle crash increased more than two-fold (odds ratio [OR] 2.3; 95% confidence interval [CI]: 1.6-3.3) and the risk of a near-miss driving event increased nearly six-fold (OR 5.9; 95% CI: 5.4-6.3) after shifts of 24 hours or greater compared with shifts of less than 24 hours. Interns were also significantly more likely to fall asleep while driving during months with one to four (OR 1.82; 95% CI: 1.73-1.93) and five or more (OR 2.39; 95% CI: 2.31-2.46) extended shifts than during months with no extended shifts. Every extended shift scheduled per month increased the monthly rate of any motor vehicle accident by 9.1 percent (95% CI: 3.4-14.7 percent) and increased the monthly rate of an accident on the commute from work by 16.2 percent (95% CI: 7.8-24.7 percent). The study authors concluded that "scheduling physicians to work such extended shifts, which our group has recently shown to increase the risk of failures of attention and serious medical errors, poses a serious and preventable safety hazard for them and other motorists."

A 2006 study of 19 residents' performance on a driving simulator found that male residents displayed greater impairment, as measured by increased lane deviations and crash frequency, after a 15-hour overnight call shift and an extra four hours in patient-care duties compared with driving simulation testing after a night spent at home without call responsibility.[27] The authors concluded that "[c]ollectively, results of this study and others suggest that medical residents are at risk when driving after a night on call."

Percutaneous injuries and exposure to blood-borne pathogens

A 2000 retrospective review analyzed 745 accidental exposures (involving both percutaneous injuries and superficial skin or mucous membrane contact from splashes) to blood-borne pathogens reported by residents and medical students while on duty.[28] The rate of such incidents was 50 percent higher during night shifts than during day shifts ($p<0.04$), and junior residents

[25] 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.
[26] 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.
[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.

(PGY-1 and PGY-2) reported considerably more such incidents than more-senior residents. The authors concluded, "Presumably, the fatigue of the 24h–36h work schedules with little or no sleep for on-call medical students and residents plus circadian rhythms in human cognitive performance and eye-hand coordination contribute to the observed day-night pattern in accidental exposures to blood-borne pathogens described herein."

A 2006 prospective cohort study analyzed reported percutaneous injuries in 2,737 interns from July 2002 through June 2003.[29] Interns most commonly reported lapses in concentration (64 percent of injuries) and fatigue (31 percent) as contributing factors for the injuries. Injuries were significantly more likely to occur during extended shifts than nonextended shifts (OR 1.61; 95% CI: 1.46-1.78). Injuries following extended shifts occurred after an average of 29 consecutive hours of work, while those occurring on days not preceded by an overnight shift occurred after an average of six hours of consecutive work. The authors concluded, "The association of these injuries with extended work duration is likely due to the adverse cognitive effects of the sleep deprivation associated with such extended work."

Depression

PGY-1 training is known to be a time of high stress, and such residents are at a higher risk for major depression than the general population.[30] A 1991 study of 61 pediatric residents (34 PGY-1 residents and 27 PGY-2 residents) found that scores on mood and anxiety questionnaires were significantly worsened following a 24-hour call shift compared with residents completing the questionnaires following 24 hours without a call shift.[31] A 1993 study found that internal medicine residents working 32-hour shifts every fourth night reported significantly higher rates of depression symptoms than those working 16-hour shifts under a night float system, as indicated on a post-shift questionnaire (although scores on anxiety and hostility questionnaires did not differ between the two groups).[32]

A 2010 prospective cohort study administered depression questionnaires to 740 PGY-1 residents at 13 U.S. hospitals.[33] Surveys were administered at one to two months prior to beginning PGY-1 training and at months 3, 6, 9, and 12 of the PGY-1 year. A total of 58 percent (740 of 1271) of the interns successfully contacted agreed to participate and, of these, 88 percent (651 of 740) completed at least one follow-up study survey. Just 4 percent of interns met the criteria for major depression at the beginning of their internship, but 27 percent reached this threshold both at month 3 and at the end of the year. The prevalence of moderately severe depression increased

[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] 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.

from 0.7 percent at baseline to 7.6 percent by the end of the year. A greater number of hours worked was significantly associated with an increase in depressive symptoms ($p<0.001$).

Obstetric outcomes

While there are no data, to our knowledge, comparing obstetric outcomes among female residents working shifts of different lengths, several surveys have indicated a possible association between residency training and poorer obstetric outcomes.

A 1990 study surveyed 5,096 female physicians who had graduated from medical school in 1985 and a random sample of 5,000 of the 12,306 male physicians who graduated the same year (response rate 85-87 percent).[34] The study found significantly increased risks of premature labor requiring bed rest or hospitalization (11.3 vs. 6.0 percent, $p<0.001$) and preeclampsia or eclampsia (8.8 vs. 3.5 percent, $p<0.001$) among female residents compared with the non-resident spouses of their male colleagues, respectively. In addition, pregnant resident physicians working 100 or more hours per week during the third trimester experienced twice the risk of preterm delivery as those working fewer than 100 hours (10.3 vs. 4.8 percent, $p=0.04$). No statistically significant differences were seen between the groups in the rates of miscarriage, ectopic gestation, stillbirths, preterm delivery, or intrauterine growth retardation.

A 2003 survey of 4,674 obstetrics and gynecology residents found statistically significantly higher rates of preterm labor (5.3 vs. 2.2 percent, $p=0.03$), preeclampsia (4.0 vs. 0.7 percent, $p=0.01$), and birth weight below the 10^{th} percentile for gestational age (3.3 vs. 0 percent, $p=0.002$) than the spouses of their male counterparts, respectively (96 percent response rate).[35]

Increased risk to experimental group resident subjects results in a lack of equipoise between the iCOMPARE trial groups

Such evidence of harm to medical residents was one of the reasons why the IOM in 2009 recommended imposing a 16-hour maximum limit on consecutive hours worked without protected sleep for *all* residents and why the ACGME in 2011 imposed such a limit for PGY-1 residents.

The risks to PGY-1 residents of being exposed repeatedly to duty shifts significantly longer 16 consecutive hours (which under the protocol could reach 30 hours or more), with reduced time off between scheduled duty shifts, greatly exceed 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

[34] Klebanoff MA, Shiono PH, Rhoads GG. Outcomes of pregnancy in a national sample of resident physicians. *N Engl J Med*. 1990;323(15):1040-1045.
[35] Gabbe SG, Morgan MA, Power ML, et al. Duty hours and pregnancy outcome among residents in obstetrics and gynecology. *Obstet Gynecol*. 2003;102(5 Pt 1):948-951.

daily life or during the performance of routine physical or psychological examinations or tests.

Importantly, the control and experimental groups in the iCOMPARE trial are not in equipoise with respect to the health of the internal medicine resident subjects. With respect to these subjects, the trial is analogous to an occupational health trial that randomly assigns workers to one of two work sites: one that complies with the upper limit of permissible exposure to a toxic chemical under current Occupational Safety and Health Administration regulations, and one that exposes the workers to two times (or higher) the upper limit of permissible exposure to that toxic chemical.

Thus, for the resident subjects in the experimental group, the trial violates the Belmont Report's basic ethical principle of beneficence[36] because the trial intervention unnecessarily exposes the subjects to avoidable risks of serious harm which do not outweigh any possible benefits of the research.

Likewise, the design and conduct of the trial fails to ensure that:

(a) The risks to the internal medicine PGY-1 resident subjects assigned to the experimental group are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, as required by HHS human subjects protection regulations at 45 C.F.R. §46.111(a)(1); and

(b) The risks to these subjects are reasonable in relation to the anticipated benefits, if any, to the subjects and the importance of the knowledge that may reasonably be expected to result, as required by HHS human subjects protection regulations at 45 C.F.R. §46.111(a)(2).

Strikingly, the publicly available documents describing the iCOMPARE trial make no mention of any potential harms that PGY-1 internal medicine resident subjects may experience if they are training at an institution randomized to the experimental group.

Finally, we can conceive of no prospective study design involving knowingly exposing PGY-1 medical residents to the dangers of extreme sleep deprivation caused by recurring duty shifts of up to 30 hours or more, with reduced time off between scheduled duty shifts, that would satisfy the Belmont Report's basic ethical principle of beneficence or the regulatory requirement that risks to subjects be minimized.

Failure to satisfy informed consent requirements

The iCOMPARE trial investigators failed to obtain and document the informed consent of the resident subjects (and the patient subjects) who are enrolled in the trial.

[36] 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 November 17, 2015.

Publicly available protocol documents describe the following as the consent procedures for the iCOMPARE trial:[37]

> Programs will complete an agreement form with DIO [designated institutional official] approval to participate. Programs will inform their [fourth-year medical student] applicants of the program's participation in iCOMPARE during the [academic year] 2015-2016 recruitment season. Trainees participating in iCOMPARE will consent by completing the study surveys.

A notification process for fourth-year medical student applicants to the internal medicine training programs participating in the iCOMPARE trial would not constitute legally effective informed consent, and even if it would, many PGY-1 residents in other medical specialties who are required to rotate on the internal medicine service (e.g., emergency medicine and psychiatry residents) are being forced to participate in the research without receiving any such notification.

Likewise, the assertion that the resident subjects will be consenting to the research by completing the study surveys is ludicrous.

In addition, according to a recent media report, the University of Pennsylvania's IRB — the designated lead IRB that reviewed and approved the iCOMPARE trial — incorrectly found that the trial involves only "minimal" risk and waived the requirements for obtaining informed consent for all subjects.[38]

The failure to obtain the informed consent of the internal medicine resident (and patient) subjects violates the Belmont Report's basic ethical principle of respect for persons.[39] Furthermore, because the experimental group interventions expose the internal medicine resident subjects to risks that far exceed minimal risk, 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, fails to comply with the requirements of HHS human subjects protection regulations at 45 C.F.R. §46.116(a).

Importantly, given the use of a cluster randomization design, obtaining the *voluntary* informed consent of all medical resident subjects who would be enrolled in a trial such as the iCOMPARE trial would never be feasible because the prospective resident subjects would be exposed to significant undue influence and coercion. Many fourth-year medical students aspiring to be

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[37] iCOMPARE trial information: Frequently asked questions. September 2014. http://www.jhcct.org/icompare/docs/iCOMPARE%20-%20Frequently%20Asked%20Questions%20%2820140908%29.pdf. Accessed November 17, 2015.

[38] Bernstein L. Some new doctors are working 30-hour shifts at hospitals around the U.S. *The Washington Post*. October 29, 2015. https://www.washingtonpost.com/national/health-science/some-new-doctors-are-working-30-hour-shifts-at-hospitals-around-the-us/2015/10/28/ab7e8948-7b83-11e5-beba-927fd8634498_story.html. Accessed November 17, 2015.

[39] 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 November 17, 2015.

internal medicine residents at prestigious training programs would be unwilling to opt out of the trial, even if informed. Also, as PGY-1 residents accepted to a residency program randomized to the experimental intervention, the subjects could not voluntarily withdraw from the research at any time without being penalized (e.g., being forced to leave the residency program).

Comment regarding the patient subjects enrolled in the iCOMPARE trial

While we have focused on the risks and lack of informed consent for the internal medicine resident subjects of the iCOMPARE trial, OHRP should also be aware that the experimental group intervention also exposes the patient subjects to greater than minimal risks, and the failure to obtain their consent is similarly a violation of the Belmont Report's basic ethical principles and the HHS human subjects protection regulations.

When the ACGME mandated in 2011 that duty periods for PGY-1 residents not exceed 16 hours (which was a significant decrease from the previous maximum of 30 hours), it offered the following cogent explanation for rejecting what the ACGME is now allowing the internal medicine resident subjects in the experimental group to do:[40]

> This group of requirements addresses the requests for some flexibility in the standards requested by the community. It takes into account the differences between PGY-1 residents and their more senior colleagues, and the consensus that very junior learners would benefit from a more supported and regulated learning environment. **PGY-1 residents may not have sufficient experience and skills to provide high-quality, safe patient care, while research indicates that under the current standards, this group works the longest hours of any cohort of residents**…. All differences between first-year and other residents, with exception of home call and 1 day off in 7, are significant ($P < .0001$). **In addition, PGY-1 residents make more errors when working longer consecutive hours. Entrusting care to residents with inadequate experience is neither good education nor quality, safe patient care. PGY-1 residents must earn the right to remain with patients for 24 continuous hours, through demonstration of the competencies required**, which are best learned under the direct supervision of upper-level residents, fellows, and faculty. The ideal is a first year of education with more protected hours, with hours and responsibilities gradually increasing over the years of residency, and the final year of residency beginning to emulate practice, while still under supervision. [Emphasis added]

Thus, patient subjects who are being enrolled in the iCOMPARE trial at hospitals affiliated with the experimental group training programs are, as acknowledged by the ACGME in 2011, being exposed to an increased risk of medical errors because of the longer duty shift hours allowed for the internal medicine resident subjects.

[40] Accreditation Council for Graduate Medical Education. *The ACGME 2011 Duty Hour Standards: Enhancing Quality of Care, Supervision, and Resident Professional Development*. 2011. https://www.acgme.org/acgmeweb/Portals/0/PDFs/jgme-monograph%5B1%5D.pdf. Accessed November 17, 2015.

Moreover, as previously noted, the trial is using a non-inferiority design.[41] As such, it is testing the null hypothesis that the patient subjects' mortality in the experimental group will be higher than that in the control group by more than a pre-specified amount (the non-inferiority margin). Rejecting the null hypothesis will require only demonstrating that the mortality rate in the experimental group's patient subjects is not significantly higher than the mortality rate in the control group's patient subjects by more than this non-inferiority margin. We note that for such trials an actual difference in mortality between the two study arms may nevertheless be deemed statistically insignificant should the upper limit of its 95 percent confidence interval fall within the allowed-for non-inferiority margin.

As explained in the next section, the iCOMPARE trial was designed in such a way that biases the trial results away from the null hypothesis. Regardless of the ultimate outcome, however, the very fact that the trial is being undertaken necessarily means that the investigators do not know whether the patient subjects in the experimental group will or will not die at a higher rate than those in the control group.

For these reasons, increased risks of medical errors and death are among the reasonably foreseeable risks of the trial for patient subjects in the experimental group.

Patient subjects being enrolled in the iCOMPARE trial at hospitals randomized to the experimental group have a right to be fully informed about, and voluntarily decide whether to be human subjects in, a research study that will expose them to an experimental intervention for which substantial evidence exists of an increased risk of medical errors.

Indeed, a 2010 survey study of a random sample of 1,200 members of the general American public revealed the following:[42]

- Respondents estimated that resident physicians currently work 12.9-hour shifts (95% CI: 12.5-13.3 hours) and 58.3-hour workweeks (95% CI: 57.3-59.3 hours).
- They believed the maximum shift duration should be 10.9 hours (95% CI: 10.6-11.3 hours) and the maximum workweek should be 50 hours (95% CI: 49.4-50.8 hours), with 1 percent approving of shifts lasting more than 24 hours (95% CI: 0.6-2 percent).
- A total of 81 percent (95% CI: 79-84 percent) believed that reducing medical resident work hours would be very or somewhat effective in reducing medical errors, and 68 percent (95% CI: 65-71 percent) favored the IOM proposal that medical residents not work more than 16 hours over an alternative IOM proposal permitting 30-hour shifts with five or more hours of protected sleep time. Overall, 81 percent believed that patients should be informed if a treating resident physician had been working for more than 24 hours, and 80 percent (95% CI: 78-83 percent) would then want a different doctor.

[41] National Institutes of Health. Research portfolio online reporting tools. Project information for 1U01HL125388-01A1. https://projectreporter.nih.gov/project_info_description.cfm?aid=8962869&icde=26807259&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC. Accessed November 17, 2015.

[42] Blum AB, Raiszadeh F, Shea S, et al. US public opinion regarding proposed limits on resident physician work hours. *BMC Medicine.* 2010;8:33. doi:10.1186/1741-7015-8-33.

Given these public opinions, few patients would voluntarily agree to be enrolled in the iCOMPARE trial should their consent, which is required under HHS human subjects protection regulations, be sought.

Flawed trial design could easily bias the results

Because the iCOMPARE trial is necessarily unblinded, there is the potential for bias to be introduced in the conduct of the trial.

One flaw in the iCOMPARE trial design that may bias it away from the null hypothesis (which, given that the iCOMPARE trial was a non-inferiority trial, is the hypothesis that the experimental arm was inferior to the control arm) is the significant variability that is allowed for implementing the experimental intervention both across internal training programs and within a particular training program over time. Again, the iCOMPARE trial is using a design nearly identical to that of the FIRST trial, which allowed significant variability in the experimental intervention as revealed in the following frequently asked question available on the FIRST trial website:[43]

> **QUESTION**: Are programs in the intervention arm required to make all of the changes specified on the table of suggested changes?
>
> **ANSWER**: No. Many common duty hour requirements have been eliminated, and we have suggested ways to revise your resident schedules and policies; however, you are not required to implement all of these changes. You can also change your resident schedules and policies throughout the year as needed. We will be asking you to report what changes have been made, and we will be monitoring what changes have been made. We would like your program to make the suggested changes, but those decisions are entirely up to you.

Hospitals that implemented fewer changes in internal medicine residents' duty schedules would be more similar to hospitals randomized to the control group intervention, making it more likely that the trial results will allow rejection of the null hypothesis and show no measurable difference in patient outcomes between the two groups.

Finally, even if all of the internal medicine training programs randomized to the experimental group had been required to strictly follow specific resident duty-hour schedules, the likelihood of detecting significant differences in the trial's patient outcome measures between the control and experimental groups is low because only a minority of the members of the internal medicine clinical care teams (i.e., the PGY-1 residents) are being exposed to significant changes in duty hours, whereas PGY-2 and above residents (internal medicine requires three years of clinical training) are being minimally affected, and supervising attending physicians, physician

[43] Flexibility in Duty Hour Requirements for Surgical Trainees Trial – "the FIRST trial"—. First trial post-randomization frequently asked questions. http://www.thefirsttrial.org/Documents/Post-Randomization%20FAQs%20(Intervention).pdf. Accessed November 17, 2015.

consultants from other specialties, nursing staff, and other ancillary clinical care staff are not being affected at all.

These factors further demonstrate that the risks to both the internal medicine resident and patient subjects in the experimental group are not reasonable in relation to the anticipated benefits, if any, to the subjects *and the importance of the knowledge that may reasonably be expected to result from this experiment*, as required by HHS human subjects protection regulations at 45 C.F.R. §46.111(a)(2).

Conclusions and requested actions

In closing, the NIH-funded iCOMPARE trial, as designed and conducted, is highly unethical and fails to materially comply with key requirements of the HHS regulations for the protection of human subjects at 45 C.F.R. Part 46. It is therefore imperative that OHRP immediately take the following actions:

(1) Invoke its authority under the OHRP-approved Federalwide Assurance (FWA)[44] for each institution engaged in the iCOMPARE trial by suspending the conduct of the trial; and

(2) Launch a compliance oversight investigation of the iCOMPARE trial and appropriately sanction all institutions engaged in the research. In conducting this investigation, we urge OHRP to address the following questions, among others:

   (a) Were the IRBs that reviewed and approved the iCOMPARE trial provided with a detailed review of the medical literature demonstrating the risks to medical residents and their patients of long medical resident duty shifts and the accompanying sleep deprivation?

   (b) Did the IRBs that approved the iCOMPARE trial review the research at a convened IRB meeting or under an expedited review procedure?

   (c) Did the IRBs that reviewed and approved the iCOMPARE trial include members who were knowledgeable about the medical literature demonstrating the risks to medical residents and their patients of long medical resident duty shifts and the accompanying sleep deprivation?

   (d) On what basis did the IRBs that reviewed and approved the iCOMPARE trial conclude that the research involved no more than minimal risk, thereby paving the way for the inappropriate waiver of the requirements for informed consent?

Furthermore, OHRP should contact the ACGME immediately and urge the organization to rescind the waiver of its 2011 duty-hour standards that permitted the unethical experimental

[44] Office for Human Research Protections. Compliance oversight procedures for evaluating institutions. October 14, 2009. http://www.hhs.gov/ohrp/compliance/evaluation/index.html. Accessed November 17, 2015.

intervention in the iCOMPARE trial to be implemented in the first place and that will continue for an extended period of time, possibly until June 2019.

Please note that OHRP may share our complaint letter, with identifiers, with anyone. Public Citizen and the American Medical Student Association today will be posting copies on their respective websites as well.

We also request an opportunity to meet with you as soon as possible to discuss additional details regarding our complaint and the need for urgent action to end this dangerous trial and protect the resident and patient subjects who are being forced to participate and placed in harm's way.

Thank you for your prompt attention to this urgent matter regarding the protection of human subjects. 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

Deborah V. Hall, M.D.
National President 2015-16
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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

Appendix
List Internal Medicine Residency Training Programs Participating in the iCOMPARE Trial and Trial Group Assignment[45]

Program Name	Intervention
Abington Memorial Hospital Program	Control
Advocate Lutheran General Hospital Program	Control
Atlantic Health (Morristown) Program	Control
Banner Good Samaritan Medical Center Program	Experimental
Baylor College of Medicine Program	Control
Baystate Medical Center/Tufts University School of Medicine Program	Experimental
Beth Israel Deaconess Medical Center Program	Control
Brigham and Women's Hospital Program	Control
Brown University Program	Control
Canton Medical Education Foundation/NEOMED Program	Control
Carilion Clinic-Virginia Tech Carilion School of Medicine Program	Experimental
Case Western Reserve University (MetroHealth) Program	Experimental
Case Western Reserve University/University Hospitals Case Medical Center Program	Experimental
Cedars-Sinai Medical Center Program	Control
Cleveland Clinic Foundation Program	Experimental
Creighton University Program	Experimental
Drexel University College of Medicine/Hahnemann University Hospital Program	Control
Duke University Hospital Program	Experimental
Eastern Virginia Medical School Program	Experimental
Emory University Program	Experimental
Geisinger Health System Program	Experimental
George Washington University Program	Experimental
Georgetown University Hospital/Washington Hospital Center Program	Control
Greater Baltimore Medical Center Program	Control
Henry Ford Hospital/Wayne State University Program	Experimental
Jackson Memorial Hospital/Jackson Health System Program	Experimental
Johns Hopkins University Program	Experimental
Johns Hopkins University/Bayview Medical Center Program	Control
Lahey Clinic Program	Experimental
Lankenau Medical Center Program	Experimental
Massachusetts General Hospital Program	Control

[45] iCOMPARE: Individualized Comparative Effectiveness of Models Optimizing Patient Safety and Resident Education: iCOMPARE participating programs. http://www.jhcct.org/icompare/listprograms.asp. Accessed November 17, 2015.

Medical College of Wisconsin Affiliated Hospitals Program	Experimental
Mercy Catholic Medical Center Program	Control
Morehouse School of Medicine Program	Experimental
Olive View/UCLA Medical Center Program	Control
Pitt County Memorial Hospital/East Carolina University Program	Experimental
St Agnes HealthCare Program	Control
St Francis Hospital of Evanston Program	Experimental
Stanford University Program	Control
Temple University Hospital Program	Experimental
Texas A&M College of Medicine-Scott and White Program	Experimental
Texas Tech University (Lubbock) Program	Control
Thomas Jefferson University Program	Control
Tufts Medical Center Program	Control
UCLA Medical Center Program	Experimental
UMDNJ Robert Wood Johnson Medical School (Camden)/Cooper University Hospital Program	Control
University Hospital/University of Cincinnati College of Medicine Program	Control
University of Colorado Denver Program	Control
University of Connecticut Program	Control
University of Kansas School of Medicine Program	Experimental
University of Maryland Program	Experimental
University of Massachusetts Program	Control
University of Nebraska Medical Center College of Medicine Program	Control
University of North Carolina Hospitals Program	Control
University of Pennsylvania Program	Experimental
University of Vermont/Fletcher Allen Health Care Program	Experimental
University of Washington Program	Experimental
UPMC Medical Education Program	Control
Virginia Commonwealth University Health System Program	Experimental
Wake Forest University School of Medicine Program	Control
Washington University/B-JH/SLCH Consortium Program	Control
West Virginia University Program	Experimental
Yale-New Haven Medical Center Program	Experimental