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November 19, 2015

Thomas J. Nasca, M.D., M.A.C.P.  
Chief Executive Officer  
Accreditation Council for Graduate Medical Education  
515 North State Street, Suite 2000  
Chicago, IL 60654

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

Dear Dr. Nasca:

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 Accreditation Council for Graduate Medical Education (ACGME) to immediately rescind the organization's waivers of most of its 2011 duty-hour standards for internal medicine and general surgery training programs randomly assigned to the experimental groups in the ongoing iCOMPARE trial and the recently completed FIRST trial, respectively.<sup>1</sup>

As discussed in detail in the enclosed complaint letters submitted today to the U.S. Department of Health and Human Services' (HHS') Office for Human Research Protections (OHRP), both trials — neither of which was possible without the ACGME waiving of its current duty-hour restriction — are highly unethical and failed to materially comply with key requirements of the HHS regulations for the protection of human subjects at 45 C.F.R. Part 46. As you can see, we are simultaneously urging OHRP to invoke its authority and immediately suspend the iCOMPARE trial.

Importantly, it seems highly unlikely that trials that involve randomizing resident physicians to the less restrictive flexible duty-hour schedule permitted under the ACGME waivers — 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 and the HHS regulations for the protection of human subjects.

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<sup>1</sup> Accreditation Council for Graduate Medical Education. Letter to members of the graduate medical education community regarding the iCOMPARE and FIRST trials. March 13, 2014. <http://www.thefirsttrial.org/Documents/2014-03-13%20Nasca%20Letter%20to%20the%20Community%20re%20Multicenter%20Duty%20Hour%20Trials.pdf>. Accessed November 17, 2015.

The 2011 work-hour restrictions were put in place because of clear evidence of risk to resident physicians and were in line with the ACGME's mission to improve health care and advance the quality of resident physicians' education.<sup>2</sup> The decision to waive most of the 2011 duty-hour standards, especially those pertaining to shift length and time off between shifts, for these studies is both shocking and deeply disappointing.

Particularly disturbing is the ACGME's apparent disregard of the evidence that justified its appropriate decision in 2011 to increase the restrictions on resident physicians' duty time, including limiting duty periods for PGY-1 residents to a maximum of 16 hours. In explaining its action, the ACGME noted the following with respect to resident health and well-being:<sup>3</sup>

- 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.

The organization similarly noted the following regarding the health and well-being of patients:<sup>4</sup>

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]

We are aware of no new evidence that refutes the evidence on long duty shifts' harmful effects on residents<sup>5</sup> and that would have justified its waivers.

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<sup>2</sup> Accreditation Council for Graduate Medical Education. ACGME Mission, Vision, and Values.

<https://www.acgme.org/acgmeweb/tabid/121/About/Mission,VisionandValues.aspx>. Accessed November 17, 2015.

<sup>3</sup> 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.

<sup>4</sup> *Ibid.*

<sup>5</sup> For a detailed summary of some of these effects, see the section within each attached letter titled "Unacceptable risk for the experimental group resident subjects."

Finally, the ACGME's decision to grant waivers that extend for a full year or more beyond the end of the one-year randomized phase of each trial is outrageous. Publicly available FIRST trial documents indicate that the ACGME waiver for general surgery residency training programs randomly assigned to the experimental arm remain in effect until June 2016, one full year after the randomized phase of the trial ended.<sup>6</sup> Likewise, several publicly available iCOMPARE documents indicate that the ACGME waiver for internal medicine residency training programs randomly assigned to the experimental arm will continue until June 2019, three full years after the randomized phase of the trial will end,<sup>7,8,9</sup> although one document indicates that the waiver will end in June 2017<sup>10</sup> (and it is also unclear, from the publicly available iCOMPARE documents, whether the waivers also apply to control arm programs). It is unethical to allow both resident physicians and patients at hospitals assigned to the experimental groups for these trials to continue to be exposed to a greater-than-minimal-risk experimental intervention after the one-year randomized phase of each trial has been completed and while data analysis is ongoing.

In closing, it is imperative that the ACGME immediately rescind the waivers of most of its 2011 duty-hour standards for the internal medicine and general surgery residency training programs randomly assigned to the experimental groups in the ongoing iCOMPARE trial and the recently completed FIRST trial, respectively. Furthermore, in light of all the concerns highlighted above and in our letters to OHRP, an independent body needs to investigate the process that allowed these inappropriate waivers to be granted in the first place, in the face of the strong evidence of resident and patient harm that caused ACGME to issue the duty-hour standards in 2011.

Thank you for your prompt attention to this urgent matter regarding the health and welfare of physician residents and patients. 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  
American Medical Student Association

<sup>6</sup> 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](http://www.thefirsttrial.org/Documents/Post-Randomization%20FAQs%20(Intervention).pdf). Accessed November 17, 2015.

<sup>7</sup> iCOMPARE trial information: Executive summary. September 2014. [http://www.jhcct.org/icompare/docs/iCOMPARE%20-%20Design%20Summary%20\(20140908\).pdf](http://www.jhcct.org/icompare/docs/iCOMPARE%20-%20Design%20Summary%20(20140908).pdf). Accessed November 17, 2015.

<sup>8</sup> iCOMPARE trial information: Frequently asked questions. [http://www.jhcct.org/icompare/docs/iCOMPARE%20-%20Frequently%20Asked%20Questions%20\(20140908\).pdf](http://www.jhcct.org/icompare/docs/iCOMPARE%20-%20Frequently%20Asked%20Questions%20(20140908).pdf). Accessed November 11, 2015.

<sup>9</sup> iCOMPARE trial information: Eligibility and program selection. September 2014. [http://www.jhcct.org/icompare/docs/iCOMPARE%20-%20Eligibility%20and%20Program%20Selection%20\(20140908\).pdf](http://www.jhcct.org/icompare/docs/iCOMPARE%20-%20Eligibility%20and%20Program%20Selection%20(20140908).pdf). Accessed November 17, 2015.

<sup>10</sup> iCOMPARE. Timeline and upcoming activities for enrolled programs. <http://www.jhcct.org/icompare/Timeline.asp>. Accessed November 17, 2015.

Public Citizen

November 19, 2015, Letter to ACGME  
Regarding the iCOMPARE and FIRST Trials

Handwritten signature of Sidney M. Wolfe in black ink.

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

Handwritten signature of Sammy Almashat in black ink.

Sammy Almashat, M.D., M.P.H.  
Researcher  
Public Citizen's Health Research Group

Enclosures

cc: Mr. John Duval, Chair, Board of Directors, ACGME  
The Honorable Sylvia Mathews Burwell, Secretary of Health and Human Services  
The Honorable Karen B. DeSalvo, Acting Assistant Secretary for Health, HHS



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November 19, 2015

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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 Borrer:

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<sup>1</sup> and were among the reasons for the ACGME’s 2011 decision to impose the current restrictions on PGY-1 medical resident duty-hour schedules.<sup>2</sup>

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<sup>3</sup> 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

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<sup>1</sup> 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.

<sup>2</sup> 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.

<sup>3</sup> 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.”<sup>4</sup> 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.<sup>5</sup>

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.<sup>6</sup> 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**<sup>7,8,9</sup>

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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<sup>4</sup> 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.

<sup>5</sup> 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](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.

<sup>6</sup> 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.

<sup>7</sup> 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.

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

<sup>9</sup> 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](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,<sup>10,11,12</sup> although one document indicates that the waiver will end in June 2017.<sup>13</sup>)

### 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:<sup>14</sup>

- 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:<sup>15</sup>

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<sup>10</sup> iCOMPARE trial information: Executive summary. September 2014.

[http://www.jhcct.org/icompare/docs/iCOMPARE%20-%20Design%20Summary%20\(20140908\).pdf](http://www.jhcct.org/icompare/docs/iCOMPARE%20-%20Design%20Summary%20(20140908).pdf). Accessed November 17, 2015.

<sup>11</sup> iCOMPARE trial information: Frequently asked questions. [http://www.jhcct.org/icompare/docs/iCOMPARE%20-%20Frequently%20Asked%20Questions%20\(20140908\).pdf](http://www.jhcct.org/icompare/docs/iCOMPARE%20-%20Frequently%20Asked%20Questions%20(20140908).pdf). Accessed November 17, 2015.

<sup>12</sup> iCOMPARE trial information: Eligibility and program selection. September 2014.

[http://www.jhcct.org/icompare/docs/iCOMPARE%20-%20Eligibility%20and%20Program%20Selection%20\(20140908\).pdf](http://www.jhcct.org/icompare/docs/iCOMPARE%20-%20Eligibility%20and%20Program%20Selection%20(20140908).pdf). Accessed November 17, 2015.

<sup>13</sup> iCOMPARE. Timeline and upcoming activities for enrolled programs.

<http://www.jhcct.org/icompare/Timeline.asp>. Accessed November 17, 2015.

<sup>14</sup> 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/acgme/Portals/0/PDFs/dh-ComparisonTable2003v2011.pdf>. Accessed November 17, 2015.

<sup>15</sup> 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/acgme/Portals/0/PDFs/jgme-monograph%5B1%5D.pdf>. Accessed November 17, 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."<sup>16</sup>

### 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:<sup>17</sup>

- 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.<sup>18</sup> For the FIRST trial experimental group, the following changes in resident duty-hour schedules were recommended by the research team:<sup>19</sup>

- 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

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<sup>16</sup> 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.

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

<sup>18</sup> Flexibility in Duty Hour Requirements for Surgical Trainees Trial – "the FIRST trial". Study overview. <http://www.thefirsttrial.org/Overview/Overview>. Accessed November 17, 2015.

<sup>19</sup> 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.<sup>20</sup>

### Outcome measures

The primary outcome measure in the iCOMPARE trial is the 30-day patient subject mortality rate.<sup>21</sup>

Secondary outcomes include measures of PGY-1 internal medicine resident subjects' education and average daily sleep.<sup>22</sup>

Importantly, the iCOMPARE trial is designed as a non-inferiority trial.<sup>23</sup> 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.<sup>24</sup>

### **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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<sup>20</sup> 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](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.

<sup>21</sup> 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](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.

<sup>22</sup> *Ibid.*

<sup>23</sup> *Ibid.*

<sup>24</sup> iCOMPARE trial information: Executive summary. September 2014.

[http://www.jhcct.org/icompare/docs/iCOMPARE%20-%20Design%20Summary%20\(20140908\).pdf](http://www.jhcct.org/icompare/docs/iCOMPARE%20-%20Design%20Summary%20(20140908).pdf). Accessed November 17, 2015.

### Motor vehicle accidents

A 1996 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.<sup>25</sup> 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.<sup>26</sup> 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.<sup>27</sup> 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.<sup>28</sup> The rate of such incidents was 50 percent higher during night shifts than during day shifts ( $p < 0.04$ ), and junior residents

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<sup>25</sup> 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.

<sup>26</sup> 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.

<sup>27</sup> 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.

<sup>28</sup> 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.<sup>29</sup> 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.<sup>30</sup> 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.<sup>31</sup> 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).<sup>32</sup>

A 2010 prospective cohort study administered depression questionnaires to 740 PGY-1 residents at 13 U.S. hospitals.<sup>33</sup> 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

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<sup>29</sup> 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.

<sup>30</sup> 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.

<sup>31</sup> Berkoff K, Rusin W. Pediatric house staff's psychological response to call duty. *J Dev Behav Pediatr*. 1991;12(1):6-10.

<sup>32</sup> 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.

<sup>33</sup> 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).<sup>34</sup> 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<sup>th</sup> percentile for gestational age (3.3 vs. 0 percent,  $p = 0.002$ ) than the spouses of their male counterparts, respectively (96 percent response rate).<sup>35</sup>

### **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

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<sup>34</sup> 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.

<sup>35</sup> 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<sup>36</sup> 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.

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<sup>36</sup> 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:<sup>37</sup>

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.<sup>38</sup>

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.<sup>39</sup> 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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<sup>37</sup> 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.

<sup>38</sup> 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](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.

<sup>39</sup> 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:<sup>40</sup>

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.

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<sup>40</sup> 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.<sup>41</sup> 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:<sup>42</sup>

- 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.

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<sup>41</sup> 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](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.

<sup>42</sup> 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:<sup>43</sup>

**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

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<sup>43</sup> 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](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)<sup>44</sup> 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

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<sup>44</sup> 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  
American Medical Student Association



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



Sammy Almashat, M.D., M.P.H.  
Researcher  
Public Citizen's Health Research Group

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

**Appendix**  
**List Internal Medicine Residency Training Programs Participating in**  
**the iCOMPARE Trial and Trial Group Assignment<sup>45</sup>**

| <b>Program Name</b>  | <b>Intervention</b> |
|--|---------------------|
| 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             |

<sup>45</sup> iCOMPARE: Individualized Comparative Effectiveness of Models Optimizing Patient Safety and Resident Education: iCOMPARE participating programs. <http://www.jhcc.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 |



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November 19, 2015

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

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

**Re: Flexibility in Duty Hour Requirements for Surgical Trainees (FIRST) Trial  
Funding: The American Board of Surgery, American College of Surgeons, Accreditation  
Council for Graduate Medical Education  
Principal Investigator: Karl Y. Bilimoria, M.D., M.S., Northwestern University  
ClinicalTrials.gov Identifier: NCT02050789**

Dear Drs. Menikoff and Borrer:

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 launch a compliance oversight investigation of the FIRST trial and appropriately sanction all institutions engaged in the trial for completely failing to protect the human subjects who were enrolled in the research. The trial, as designed and conducted, was highly unethical and failed to materially comply with essentially all 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 were as follows:

- (1) Under the FIRST trial protocol, first year (PGY-1) general surgery residents at approximately 160 hospitals (or hospital systems) across the U.S. (see Appendix) were randomly assigned to one of the following two interventions in their work treating patients at these hospitals:

- (a) A “usual care” duty-hour schedule that complied 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 allowed duty shifts of unlimited duration; these shifts could have reached 28 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 knowingly exposed 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<sup>1</sup> and were among the reasons for the ACGME’s 2011 decision to impose the current restrictions on PGY-1 medical resident duty-hour schedules.<sup>2</sup>

Therefore, the control and experimental groups in the trial were not in equipoise with respect to the health of the general surgery resident subjects. For the experimental group subjects, the trial violated the Belmont Report’s basic ethical principle of beneficence<sup>3</sup> because the trial intervention unnecessarily exposed them to known, avoidable risks of serious harm which did not outweigh any possible benefits of the research. Likewise, the design and conduct of the trial failed to ensure that (a) the risks to the general surgery PGY-1 resident subjects in the experimental group were minimized by using procedures that were consistent with sound research design and that did 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 were 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 institutional review board (IRB) at Northwestern University, the lead institution for the FIRST trial, determined that the FIRST trial did “not constitute research with human subjects in accordance with 45 CFR 46” and, therefore, that IRB approval was not required.<sup>4</sup> This determination represents a colossal failure of Northwestern University’s

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<sup>1</sup> 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.

<sup>2</sup> 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.

<sup>3</sup> 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.

<sup>4</sup> Northwestern University Institutional Review Board Office. Completed form for determining whether a project involves human subjects research (version 3.0) for the FIRST trial. Signed November 21, 2013.



human subjects protection system. This same failure presumably occurred at many — perhaps most — of the other institutions engaged in the FIRST trial.

- (3) The investigators failed to obtain and document the informed consent of the general surgery resident subjects and the patient subjects who were enrolled in this experiment.

The failure to obtain the informed consent of the general surgery resident subjects (and of the patient subjects as well) first and foremost violated the Belmont Report's basic ethical principle of respect for persons.<sup>5</sup> Furthermore, as discussed in (1) above, the experimental group intervention exposed the general surgery resident subjects to risks that far exceeded 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 failed 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 FIRST trial, its serious ethical and regulatory failings, and our requested actions.

### **FIRST trial design**<sup>6,7,8</sup>

The FIRST trial used cluster randomization. One hundred sixty-six hospitals affiliated with general surgery residency training programs across the U.S. 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). According to the FIRST trial's website, the trial interventions started on July 1, 2014, and continued until June 30, 2015. An ACGME waiver of its 2011 duty-hour standards for all FIRST trial experimental group training programs,

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<http://www.thefirsttrial.org/Documents/FIRST%20Trial%20IRB%20Non-Human%20Subjects%20Determination.pdf>. Accessed November 17, 2015.

<sup>5</sup> 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.

<sup>6</sup> ClinicalTrials.gov. Flexibility In Duty Hour Requirements for Surgical Trainees Trial - "the FIRST Trial" NCT02050789. <https://clinicaltrials.gov/ct2/show/NCT02050789?term=NCT02050789&rank=1>. Accessed November 17, 2015.

<sup>7</sup> Flexibility in Duty Hour Requirements for Surgical Trainees Trial – “the FIRST trial”. Study overview.

<http://www.thefirsttrial.org/Overview/Overview>. Accessed November 11, 2015.

<sup>8</sup> The Flexibility in Duty Hour Requirements for Surgical Trainees Trial: Statistical analysis plan. Updated version April 2015.

<http://www.thefirsttrial.org/Documents/FIRST%20Trial%20Statistical%20Analysis%20Protocol%20Updated%20APRIL2015.pdf>. Accessed November 17, 2015.

which allowed the investigators to conduct the trial, inexplicably remains in effect until June 2016, a full year following the end of the one-year randomized experiment.<sup>9</sup>

### Control group intervention

For the hospitals assigned to the control group intervention, resident duty-hour schedules had to 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:<sup>10</sup>

- 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:<sup>11</sup>

- 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

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<sup>9</sup> 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](http://www.thefirsttrial.org/Documents/Post-Randomization%20FAQs%20(Intervention).pdf). Accessed November 17, 2015.

<sup>10</sup> 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.

<sup>11</sup> 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.

16 hours unless a 5-hour uninterrupted continuous sleep period is provided between 10 p.m. and 8 a.m.”<sup>12</sup>

### Experimental group intervention

For the hospitals assigned to the experimental group intervention, residents were 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 were eliminated, and only three rules applied:<sup>13,14</sup>

- 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.

For the FIRST trial experimental group, the following changes in resident duty-hour schedules were recommended by the research team:<sup>15</sup>

- 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 FIRST trial’s experimental group intervention allowed for extensions of duty shift duration and decreases in time off between scheduled duty periods for general surgery residents at all training levels (PGY-1 and above) beyond those permitted under current ACGME requirements, it is clear that PGY-1 general surgery resident subjects were exposed to the greatest increased risk. Under the trial protocol, the maximum duty shift duration for PGY-1 residents could routinely have been increased from the ACGME-mandated maximum of 16 hours to 28 hours or more.

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<sup>12</sup> 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.

<sup>13</sup> Flexibility in Duty Hour Requirements for Surgical Trainees Trial – “the FIRST trial”. Study overview. <http://www.thefirsttrial.org/Overview/Overview>. Accessed November 17, 2015.

<sup>14</sup> The Flexibility in Duty Hour Requirements for Surgical Trainees Trial: Statistical analysis plan. Updated version April 2015. <http://www.thefirsttrial.org/Documents/FIRST%20Trial%20Statistical%20Analysis%20Protocol%20Updated%20APRIL2015.pdf>. Accessed November 17, 2015.

<sup>15</sup> FIRST trial recommendations for intervention arm hospitals. <http://www.thefirsttrial.org/Documents/Summary%20of%20Suggested%20Intervention%20Arm%20Changes.pdf>. Accessed November 17, 2015.

### Outcome measures

Publicly available documents for the FIRST trial contain discrepancies regarding the prespecified primary outcome measure for the patient subjects. Documents available on the FIRST trial website indicate that the primary outcome was 30-day postoperative death or serious morbidity.<sup>16</sup> In contrast, the entry for the trial on the ClinicalTrials.gov website states that the primary outcome measure was the 30-day patient-subject death rate.<sup>17</sup>

Documents available on the FIRST trial website indicate that the secondary patient outcomes included the following, among others: 30-day postoperative death, 30-day postoperative morbidity, 30-day postoperative surgical site infection, 30-day postoperative myocardial infarction, 30-day postoperative unplanned return to operating room, and non-discharge to home,<sup>18</sup> whereas the entry for the trial on the ClinicalTrials.gov website states that the sole secondary outcome measure for patient subjects was 30-day serious morbidity.<sup>19</sup>

The primary outcomes for the resident subjects were general satisfaction with the quality of residency education and overall satisfaction with well-being. Secondary outcomes for these subjects included, among others, perceived safety of patient care, perceived continuity of care, attendance at educational conferences, acquisition of clinical skills, job satisfaction, morale, self-reported health, self-reported rest, self-reported well-being, and fatigue.<sup>20</sup> These outcomes were measured by a survey instrument administered to the general surgery resident subjects once in January 2015, a point when the trial was only a little more than halfway completed.

Importantly, the FIRST trial was designed as a non-inferiority trial.<sup>21</sup> The researchers were seeking to demonstrate that the composite primary outcome of 30-day postoperative death or serious morbidity in the experimental group patient subjects would 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 was that the rate of this composite patient outcome in the experimental group would be higher than that in the control group by more than this non-

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<sup>16</sup> The Flexibility in Duty Hour Requirements for Surgical Trainees Trial: Statistical analysis plan. Updated version April 2015.

<http://www.thefirsttrial.org/Documents/FIRST%20Trial%20Statistical%20Analysis%20Protocol%20Updated%20APRIL2015.pdf>. Accessed November 17, 2015.

<sup>17</sup> ClinicalTrials.gov. Flexibility In Duty Hour Requirements for Surgical Trainees Trial - "the FIRST Trial", NCT02050789. <https://clinicaltrials.gov/ct2/show/NCT02050789?term=NCT02050789&rank=1>. Accessed November 17, 2015.

<sup>18</sup> The Flexibility in Duty Hour Requirements for Surgical Trainees Trial: Statistical analysis plan. Updated version April 2015.

<http://www.thefirsttrial.org/Documents/FIRST%20Trial%20Statistical%20Analysis%20Protocol%20Updated%20APRIL2015.pdf>. Accessed November 17, 2015.

<sup>19</sup> ClinicalTrials.gov. Flexibility In Duty Hour Requirements for Surgical Trainees Trial - "the FIRST Trial" NCT02050789. <https://clinicaltrials.gov/ct2/show/NCT02050789?term=NCT02050789&rank=1>. Accessed November 17, 2015.

<sup>20</sup> The Flexibility in Duty Hour Requirements for Surgical Trainees Trial: Statistical analysis plan. Updated version April 2015.

<http://www.thefirsttrial.org/Documents/FIRST%20Trial%20Statistical%20Analysis%20Protocol%20Updated%20APRIL2015.pdf>. Accessed November 17, 2015.

<sup>21</sup> *Ibid.*

inferiority margin, which was defined as an absolute difference of 1.25 percentage points (which, given the investigators' estimate that 9.94 percent of control group patient subjects would experience the primary outcome, is equivalent to a relative difference of 12.6 percentage points).<sup>22</sup>

### **Unacceptable risk for the experimental group general surgery 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.

#### Motor vehicle accidents

A 1996 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.<sup>23</sup> 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.<sup>24</sup> 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

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<sup>22</sup> *Ibid.*

<sup>23</sup> 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.

<sup>24</sup> 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.

driving simulation testing after a night spent at home without call responsibility.<sup>25</sup> 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.<sup>26</sup> The rate of such incidents was 50 percent higher during night shifts than during day shifts ( $p < 0.04$ ), and junior residents (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.<sup>27</sup> 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.<sup>28</sup> 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.<sup>29</sup> 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

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<sup>25</sup> 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.

<sup>26</sup> 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.

<sup>27</sup> 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.

<sup>28</sup> 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.

<sup>29</sup> Berkoff K, Rusin W. Pediatric house staff's psychological response to call duty. *J Dev Behav Pediatr*. 1991;12(1):6-10.

indicated on a post-shift questionnaire (although scores on anxiety and hostility questionnaires did not differ between the two groups).<sup>30</sup>

A 2010 prospective cohort study administered depression questionnaires to 740 PGY-1 residents at 13 U.S. hospitals.<sup>31</sup> 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 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).<sup>32</sup> 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<sup>th</sup> percentile for gestational age (3.3 vs. 0 percent,  $p = 0.002$ ) than the spouses of their male counterparts, respectively (96 percent response rate).<sup>33</sup>

### **Increased risks to experimental group general surgery resident subjects resulted in a lack of equipoise between the FIRST trial groups**

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<sup>30</sup> 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.

<sup>31</sup> 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.

<sup>32</sup> 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.

<sup>33</sup> 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.

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 than 16 consecutive hours (which under the protocol could reach 30 hours or more), with reduced time off between scheduled duty shifts, greatly exceeded 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.

Importantly, the control and experimental groups in the FIRST trial were not in equipoise with respect to the health of the general surgery resident subjects. With respect to these subjects, the trial was 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 (or more) times the upper limit of permissible exposure to that toxic chemical.

Thus, for the resident subjects in the experimental group, the trial violated the Belmont Report's basic ethical principle of beneficence<sup>34</sup> because the trial intervention unnecessarily exposed 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 failed to ensure that:

- (a) The risks to the general surgery PGY-1 resident subjects assigned to the experimental group were 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 were 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).

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<sup>34</sup> 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>. November 17, 2015.



Strikingly, the publicly available documents describing the FIRST trial make no mention of any potential harms that PGY-1 general surgery resident subjects could have experienced if they were 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.

### **Lack of IRB review and approval**

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 FIRST trial 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 general surgery residents at hospitals engaged in the FIRST trial and their patients obviously were human subjects of the research. The researchers intervened with both groups at the hospitals randomized to the experimental group by manipulating the duty schedules of the general surgery residents for research purposes. The researchers also appear to have interacted with the general surgery residents through research-specific surveys.<sup>35</sup>

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<sup>35</sup> Flexibility in Duty Hour Requirements for Surgical Trainees Trial — “the FIRST trial”. Study overview. <http://www.thefirsttrial.org/Overview/Overview>. Accessed November 17, 2015.

HHS human subjects protection regulations at 45 C.F.R. §46.101(b) describe six categories of human subjects research that are exempt from the regulations. The FIRST trial was not eligible for any of these exemptions.

The fact that the FIRST trial represented non-exempt human subjects research should have been immediately obvious to anyone with even a basic understanding of the HHS human subjects protection regulations. And yet, remarkably, the manager of the Social and Behavioral Sciences IRB at Northwestern University, the lead institution for the FIRST trial, determined that the trial did “not constitute research with human subjects in accordance with 45 CFR 46” and that, therefore, IRB review and approval was not required.<sup>36</sup> This determination represents a colossal failure of Northwestern University’s human subjects protection system. This same failure presumably occurred at many of the other institutions engaged in the FIRST trial. As a result of these failures, the FIRST trial failed to comply with essentially all of the requirements of the HHS human subjects protection regulations, and the human subjects enrolled in the trial were not afforded the protections that they deserved.

It is urgent that OHRP immediately find out how many other IRBs followed the Northwestern University IRB’s lead and made the same serious blunder.

### **Failure to satisfy informed consent requirements**

The FIRST trial investigators failed to obtain and document the informed consent of the resident subjects (and the patient subjects) who were forced to enroll in the trial. It is also unclear whether fourth-year medical students who applied to be PGY-1 residents in the general surgery residency programs that participated in the FIRST trial were provided with any notice about the research (although such notice would not have constituted legally effective informed consent).

The failure to obtain the informed consent of the general surgery resident (and patient) subjects violated the Belmont Report’s basic ethical principle of respect for persons.<sup>37</sup> Furthermore, because the experimental group interventions exposed the general surgery resident subjects to risks that far exceed minimal risk, the trial would not have been eligible for a waiver of the requirement for obtaining the informed consent of all subjects, and the conduct of the trial, therefore, failed to comply with the requirements of 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 FIRST 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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<sup>36</sup> Northwestern University Institutional Review Board Office. Completed form for determining whether a project involves human subjects research (version 3.0) for the FIRST trial. Signed November 21, 2013. <http://www.thefirsttrial.org/Documents/FIRST%20Trial%20IRB%20Non-Human%20Subjects%20Determination.pdf>. Accessed November 17, 2015.

<sup>37</sup> 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.

general surgery 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 FIRST trial**

While we have focused on the risks and lack of informed consent for the general surgery resident subjects of the FIRST trial, OHRP should also be aware that the experimental group intervention also exposed the patient subjects to greater than minimal risks, and the failure to obtain their consent was 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 must 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 allowed the general surgery resident subjects in the experimental group to do:<sup>38</sup>

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 were enrolled in the FIRST trial at hospitals randomized to the experimental group were, as acknowledged by the ACGME in 2011, exposed to an increased risk of medical errors because of the longer duty shift hours allowed for the general surgery resident subjects.

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<sup>38</sup> 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 FIRST trial used a non-inferiority design. As such, it was testing the null hypothesis that the rate of the composite primary patient outcome of 30-day postoperative death or serious morbidity in the experimental group would be higher than that in the control group by an absolute difference of at least 1.25 percentage points (the non-inferiority margin, equivalent in this trial to a relative difference of at least 12.6 percentage points). Rejecting the null hypothesis required only demonstrating that the rate of this primary outcome in the experimental group's patient subjects was not significantly higher than that in the control group's patient subjects by more than this non-inferiority margin. We note that for such trials an actual difference in the combined 30-day mortality and serious morbidity between the two study arms would 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 FIRST trial was designed in such a way that biased the trial results away from the null hypothesis. Regardless of the ultimate outcome, however, the very fact that the trial was undertaken necessarily means that the investigators did not know whether the patient subjects in the experimental group would or would not die or suffer serious morbidity at a higher rate than those in the control group.

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

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

Indeed, a published 2010 survey study of a random sample of 1,200 members of the general American public revealed the following.<sup>39</sup>

- 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.

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<sup>39</sup> 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 have voluntarily agreed to be enrolled in the FIRST trial had their consent, which was required under HHS human subjects protection regulations, been sought.

### **The FIRST trial investigators' agenda and flawed trial design could easily have biased the results**

Since before the FIRST trial began, the investigators who designed the trial have been very transparent about their agenda and underlying biases: It appears that their primary goal is to have the ACGME rescind its 2011 duty-hour requirements that placed more restrictive limits on maximum duty period length and minimum time off between scheduled duty periods for all residents, but particularly those affecting PGY-1 residents. And to achieve this goal, they believe they only need the FIRST study to show no significant differences in the primary and secondary patient outcomes, which is the most likely result given the flawed study design.

For example, a slide presentation that was used to promote the FIRST trial and solicit the participation of general surgery residency training programs had a slide titled "Expected Results" that included the following bullet points:<sup>40</sup>

- No difference in outcomes
- Return to more flexible resident duty hours
- Culture change: Emphasize continuity of care, not clocking in/out

Another slide titled "Why Should You Join?" included the following bullets:<sup>41</sup>

- Minimal work for you
- Huge opportunity to influence resident duty hour requirements
- Need everyone to participate if we are to generate high-level, compelling evidence

Because the FIRST trial was necessarily unblinded, such communications of the lead investigators' strongly desired and expected results may have undermined the conduct of the trial in a manner that biased the final results away from the null hypothesis (which, given that the FIRST trial was a non-inferiority trial, would be the hypothesis that the experimental arm was inferior to the control arm).

Another flaw in the FIRST trial design that may have further biased it away from the null hypothesis was the significant variability that was allowed for implementing the experimental intervention both across general surgery training programs and within a particular institution

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<sup>40</sup> Flexibility in Duty Hour Requirements for Surgical Trainees Trial – "the FIRST trial": Webinar PowerPoint presentation.

<http://www.thefirsttrial.org/Documents/Flexibility%20In%20duty%20hour%20Requirements%20for%20Surgical%20Trainees%20Trial-the%20FIRST%20trial%20webinar.pptx>. Accessed November 17, 2015.

<sup>41</sup> *Ibid.*

over time, as revealed in the following frequently asked question available on the FIRST trial website:<sup>42</sup>

**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 general surgery residents' duty schedules than those recommended under the protocol would have been 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 hospitals randomized to the experimental group had been required to strictly follow all of the suggested changes for the 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 general surgery clinical care teams (i.e., the PGY-1 residents) were exposed to significant changes in duty hours, whereas PGY-2 and above residents (general surgery requires five years of clinical training<sup>43</sup>) were minimally affected, and supervising attending physicians, physician consultants from other specialties, nursing staff, and other ancillary clinical care staff were not affected at all.

These factors further demonstrate that the risks to both the general surgery resident and patient subjects in the experimental group were not reasonable in relation to the anticipated benefits, if any, to the subjects *and the importance of the knowledge that may reasonably have been 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 FIRST trial, as designed and conducted, was highly unethical and failed to materially comply with essentially all requirements of the HHS regulations for the protection of human subjects at 45 C.F.R. Part 46. It is therefore imperative that OHRP launch a compliance

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<sup>42</sup> 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](http://www.thefirsttrial.org/Documents/Post-Randomization%20FAQs%20(Intervention).pdf). Accessed November 17, 2015.

<sup>43</sup> American College of Surgeons. How many years of postgraduate training do surgical residents undergo? <https://www.facs.org/education/resources/medical-students/faq/training>. Accessed November 17, 2015.

oversight investigation of the FIRST trial for all institutions that were engaged in the research and appropriately sanction them.

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 intervention in the FIRST trial to be implemented in the first place and that will continue until June 2016.

Even if the involved institutions have not voluntarily extended their OHRP-approved Federalwide Assurances (FWAs) to all research regardless of sponsorship, OHRP must determine how such failures occurred, because these circumstances likely signal serious systemic failures that extend to human subjects research that is federally funded and covered by their FWAs.

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 a copy 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.

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  
American Medical Student Association



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

A handwritten signature in black ink, appearing to be 'SA' with a flourish.

Sammy Almashat, M.D., M.P.H.  
Researcher  
Public Citizen's Health Research Group

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



**Appendix**  
**List of Hospitals That Participated in the FIRST Trial<sup>44</sup>**

Below is a list of the 152 ACS-NSQIP hospitals that have elected to participate in the FIRST trial (hospitals marked with an asterisk also appear on the list of 14 MSQC hospitals below):

Abington Memorial Hospital  
Alegent Creighton Health, Creighton University Medical Center  
Baptist Memorial Hospital Memphis  
Barnes-Jewish Hospital at Washington University Medical Center  
Barnes-Jewish West County Hospital  
Baylor University Medical Center  
Baystate Medical Center  
Beaumont Hospital Grosse Pointe\*  
Beth Israel Deaconess Medical Center  
Brigham & Women's Hospital  
Brigham and Women's Faulkner Hospital  
Bronson Methodist Hospital\*  
Carilion Clinic/Carilion Medical Center  
Carle Foundation Hospital  
Carolinas Medical Center  
Christiana Care Health System  
Cleveland Clinic Foundation  
Cooper University Hospital  
Dallas County Hospital District d/b/a Parkland Health & Hospital System  
Danbury Hospital  
Dartmouth-Hitchcock Medical Center  
Duke University Hospital  
Eisenhower Army Medical Center  
Emory University Hospital  
Erlanger Health System at Chattanooga  
Exempla Saint Joseph Hospital  
Fletcher Allen Health Care - Hospital  
George Washington University Hospital  
Good Samaritan Hospital (TriHealth)  
Gundersen Lutheran Medical Center  
Hackensack University Medical Center  
Hahnemann University Hospital  
Hartford Hospital  
Hennepin County Medical Center  
Henry Ford Hospital\*  
Hospital of the University of Pennsylvania  
Houston Methodist Hospital

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<sup>44</sup> Flexibility in Duty Hour Requirements for Surgical Trainees Trial – “the FIRST trial”. Enrolled hospitals. <http://www.thefirsttrial.org/Hospitals/Hospitals>. Accessed November 17, 2015.

Indiana University Health - Methodist Hospital  
Indiana University Hospital, IU Health  
Inova Fairfax Hospital  
Intermountain Medical Center  
Iowa Methodist Medical Center  
Johns Hopkins Hospital  
Kaiser Foundation Hospital Oakland  
Kaiser Foundation Hospital Sacramento  
Kaiser Permanente San Francisco Medical Center  
Kaiser Permanente Santa Clara Medical Center  
Kaiser Sunnyside Medical Center  
Kapiolani Medical Center for Women & Children  
Lahey Clinic  
Legacy Emanuel Hospital & Health Center  
Legacy Good Samaritan Medical Center  
Maine Medical Center  
Massachusetts General Hospital  
Mayo Clinic Arizona d/b/a Mayo Clinic Hospital  
Mayo Clinic Hospital Rochester - Methodist Campus  
Mayo Clinic Rochester – Saint Marys Campus  
Medical Center of Central Georgia  
Medical University Hospital Authority  
Memorial Health University Medical Center  
Memorial Hermann Hospital - TMC  
Memorial Hermann Southwest  
Memorial Medical Center  
Mercy Medical Center (Des Moines, IA)  
Meriter Hospital  
Methodist University Hospital  
MetroHealth Medical Center  
Morristown Medical Center  
Mountain States Health Alliance d/b/a Johnson City Medical Center  
Naval Medical Center Portsmouth, Virginia  
New Hanover Regional Medical Center  
Newark Beth Israel Medical Center  
Newton-Wellesley Hospital  
Northwestern Memorial Hospital  
Ochsner Clinic Foundation  
Oregon Health & Science University  
Orlando Regional Medical Center (FSCI)  
OSF Saint Francis Medical Center  
Penn State Milton S. Hershey Medical Center  
Pennsylvania Hospital, UPHS  
Providence Portland Medical Center  
Providence St. Vincent Medical Center  
Rhode Island Hospital

Riverside County Regional Medical Center  
Robert Packer Hospital  
Ronald Reagan UCLA Medical Center  
Rush University Medical Center  
Saint Francis Hospital - Memphis, TN  
Saint Francis Hospital & Medical Center  
Saint Joseph Mercy Hospital\*  
Saint Louis University Hospital  
Saint Mary's Hospital (CT)  
Saint Thomas West Hospital  
Saint Vincent Hospital - Indianapolis  
Santa Barbara Cottage Hospital  
Scott & White Hospital  
Sinai Hospital of Baltimore  
Sparrow Hospital\*  
Spectrum Health Hospitals\*  
Stamford Hospital  
Stanford Hospital and Clinics  
Straub Clinic and Hospital  
Sutter West Bay Hospitals d/b/a California Pacific Medical Center  
Tampa General Hospital (FSCI)  
Tarrant County Hosp District / JPS Health Network  
Temple University Hospital  
The Christ Hospital  
The Hospital of Central Connecticut  
The Jewish Hospital  
The Miriam Hospital  
The Nebraska Medical Center  
The Ohio State University Wexner Medical Center  
The Queen's Medical Center  
The Regional Medical Center at Memphis  
Thomas Jefferson University Hospital  
Truman Medical Center  
Tufts Medical Center  
UF Health Jacksonville (FSCI)  
UMass Memorial Medical Center  
UNC Hospitals  
University Hospital (Newark, NJ)  
University Hospital (San Antonio, TX)  
University of Alabama at Birmingham Hospital  
University of California Davis Medical Center  
University of California Irvine Medical Center  
University of California San Francisco Medical Center  
University of Colorado Hospital  
University of Connecticut Health Center Finance Corp On behalf of John Dempsey  
Hospital

University of Iowa Hospitals and Clinics  
 University of Kansas Hospital - Kansas City, KS  
 University of Kentucky Hospital  
 University of Maryland Medical Center  
 University of Minnesota Medical Center, Fairview  
 University of Missouri Hospital  
 University of Tennessee Medical Center-Knoxville  
 University of Texas M.D. Anderson Cancer Center  
 University of Texas Medical Branch  
 University of Utah Hospitals and Clinics  
 University of Virginia Health System at Charlottesville  
 University of Washington Medical Center  
 University of Wisconsin Hospital & Clinics  
 UPMC Presbyterian  
 UT Southwestern University Hospital  
 Vanderbilt University Hospital  
 Vidant Medical Center  
 Wake Forest Baptist Health  
 Wellmont Bristol Regional Medical Center  
 West Virginia University Hospitals  
 William Beaumont Hospital (Royal Oak)\*  
 Winchester Medical Center  
 Womack Army Medical Center  
 York Hospital

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Below is a list of the 14 MSQC hospitals that have elected to participate in the FIRST trial (hospitals marked with an asterisk also appear on the list of 152 ACS-NSQIP hospitals above):

Beaumont Hospital Grosse Pointe\*  
 Bronson Methodist Hospital\*  
 Detroit Receiving Hospital  
 Harper University Hospital  
 Henry Ford Hospital\*  
 Huron Valley Hospital  
 Providence Hospital and Medical Centers  
 Sinai Grace Hospital  
 Sparrow Hospital\*  
 Spectrum Health Butterworth\*  
 St. John Hospital and Medical Center  
 St. Joseph Mercy Hospital\*  
 University of Michigan Health System  
 William Beaumont Hospital (Royal Oak)\*