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November 19, 2015

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Kristina Borrer, Ph.D.
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**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 report¹ and were among the reasons for the ACGME’s 2011 decision to impose the current restrictions on PGY-1 medical resident duty-hour schedules.²

Therefore, the control and experimental groups in the 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 beneficence³ 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.⁴ This determination represents a colossal failure of Northwestern University’s

¹ Institute of Medicine. *Resident Duty Hours: Enhancing Sleep, Supervision, and Safety*. Washington, DC: The National Academies Press; 2009. <http://www.nap.edu/catalog/12508/resident-duty-hours-enhancing-sleep-supervision-and-safety>. Accessed November 17, 2015.

² Accreditation Council for Graduate Medical Education. *The ACGME 2011 Duty Hour Standards: Enhancing Quality of Care, Supervision, and Resident Professional Development*. 2011. <https://www.acgme.org/acgme/web/Portals/0/PDFs/jgme-monograph%5B1%5D.pdf>. Accessed November 17, 2015.

³ National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. April 18, 1979. <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>. Accessed November 17, 2015.

⁴ 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.⁵ 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^{6,7,8}

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,

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

⁵ 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.

⁶ 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.

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

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

⁸ 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.⁹

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:¹⁰

- 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:¹¹

- 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

⁹ 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.

¹⁰ 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.

¹¹ 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.”¹²

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:^{13,14}

- 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:¹⁵

- 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.

¹² 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.

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

¹⁴ 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.

¹⁵ 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.¹⁶ 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.¹⁷

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,¹⁸ 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.¹⁹

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.²⁰ 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.²¹ 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-

¹⁶ 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.

¹⁷ 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.

¹⁸ 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.

¹⁹ 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.

²⁰ 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.

²¹ *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).²²

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.²³ 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.²⁴ 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

²² *Ibid.*

²³ 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.

²⁴ 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.²⁵ 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.²⁶ 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 2003.²⁷ 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.²⁸ 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.²⁹ 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

²⁵ 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.

²⁶ 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.

²⁷ 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.

²⁸ 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.

²⁹ 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).³⁰

A 2010 prospective cohort study administered depression questionnaires to 740 PGY-1 residents at 13 U.S. hospitals.³¹ 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).³² 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 10th percentile for gestational age (3.3 vs. 0 percent, $p = 0.002$) than the spouses of their male counterparts, respectively (96 percent response rate).³³

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

³⁰ 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.

³¹ 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.

³² 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.

³³ 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 beneficence³⁴ 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).

³⁴ 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.³⁵

³⁵ 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.³⁶ 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.³⁷ 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

³⁶ 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.

³⁷ 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:³⁸

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.

³⁸ 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.³⁹

- 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.

³⁹ 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:⁴⁰

- 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:⁴¹

- 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

⁴⁰ 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.

⁴¹ *Ibid.*

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

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 training⁴³) 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

⁴² 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.

⁴³ 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 long horizontal stroke extending to the left.

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 Trial⁴⁴

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

⁴⁴ 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

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)*