DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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July 19, 2007

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Donald M. Steinwachs, PhD
Institutional Official
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Eaton E. Lattman, Ph.D.
Dean for Research
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Office of the Dean
237 Mergenthaler Hall
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RE: Human Research Protections Under Federalwide Assurances FWA-5752, FWA-287, and FWA-3834

Research Publication: Peter Pronovost, Dale Needham, Sean Berenholtz, David Sinopoli, Haitao Chu, Sara Cosgrove, Bryan Sexton, et. al. An Intervention to Decrease Catheter-Related Bloodstream Infections in the ICU. New England Journal of Medicine 2006; 355: 2725-2732.

Dear Drs. Ford, Steinwachs, and Lattman:

The Office for Human Research Protections (OHRP) has reviewed the Johns Hopkins

University (JHU) institutions' March 30, 2007 letter responding to allegations of non-compliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46).

Based upon its review, OHRP makes the following determinations regarding the research described in the above-reference publication:

(1) In accordance with HHS regulations at 45 CFR 46.103(a), each institution engaged in non-exempt research conducted or supported by HHS must provide written assurance satisfactory to the Secretary of HHS that it will comply with the requirements of HHS regulations at 45 CFR part 46. In accordance with the terms of your institutions' FWAs, when an institution holding an FWA is either (a) the primary awardee under an HHS grant, contract, or cooperative agreement supporting research to which the FWA applies, or (b) the coordinating center for HHS-conducted or –supported research to which the FWA applies, that institution is responsible for ensuring that all collaborating institutions engaged in such research operate under an appropriate OHRP-approved assurance for the protection of human subjects. Furthermore, in accordance with HHS regulations at 45 CFR 46.103(b) and 46.109(a), an institutional review board (IRB) designated under an OHRP-approved assurance must review and approve all non-exempt human subject research covered by the assurance.

The JHU institutions assert that the research project described in the above-referenced publication as carried out by JHU was exempt and that the interventions carried by the Michigan hospitals were not human subjects research, but quality improvement. OHRP notes the following from your March 30, 2007 response and the above-referenced publication:

(a) The "Exempt Research Application Form" submitted to the JHU institutional review board (IRB), in the section marked "Indicate where this study will be conducted:" and the principal investigator marked "Other: Michigan Hospitals Association and participating hospitals" indicating that the research was to be conducted at multiple institutions in Michigan. "The Johns Hopkins Hospital" had also been checked off but appeared to be partially obscured with white-out.

(b) The application to the IRB stated:

> We hypothesize that we can improve patient safety; improve safety culture; and reduce [intensive care unit] ICU mortality, blood stream infections, aspiration pneumonia and ICU

> length of stay. To accomplish this we will partner with the Michigan Hospital Association, whose [sic] has over 130 Michigan hospitals, to implement a safety program and other interventions in a cohort of hospitals. The specific aims of this project are to implement and evaluate the (1) impact of the Comprehensive Unit-based Safety Program that includes the ICU Safety Reporting System; (2) effect of an intervention to improve communication and staffing in ICUs; (3) effect of an intervention to reduce/eliminate catheter related blood stream infections in ICUs: (4) effect of an intervention to improve the care of ventilated IC patients; and (5) effect of an intervention to reduce ICU mortality. To implement these aims, we will develop interventions for MHA who will then interact with Michigan hospitals to implement these interventions.

The Grant Application to the Agency for Healthcare Research and Quality (AHRQ) stated almost identical hypotheses and aims. This indicates that the interventions were developed by JHU and were implemented by the Michigan hospitals, in part, to evaluate the impact of interventions on patient safety at these hospitals.

(c) The application to the IRB also stated:

> "This project will involve human subjects at the participating ICUs in Michigan….The study in this proposal does not involve significant physical or mental risk to subjects. The surveys pose minimal time and emotional burden on staff. The intervention is targeted to providers to improve patient safety in the ICU through the use of an error reporting system and through implementing interventions that improve patient safety and represent "best practice. [sic]….In addition, we will have a steering committee that will be charged with yearly review of accumulating data on risks and benefits of the intervention to assure that no patient is knowingly subjected to excess risk or prevented from receiving beneficial treatment."

This statement indicates that human subjects research was to be carried out at the Michigan hospitals and that care would be changed as a direct result of the research.

(d) The principal investigator requested exemption under exemption 5 (HHS regulations at 45 CFR 46.101(b)(5)); the JHU IRB approved the project as exempt under exemption 4 (HHS regulations at 45 CFR 46.101(b)(4)). However, exemption 4 only applies to research involving the collection or study of existing data, documents, records, records, pathological specimens, or diagnostic specimens if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. OHRP notes that the research proposed in the application to the JHU IRB and described in the above-referenced publication involved testing an intervention in the ICU setting and not just the collection or study of data, documents, or records, and the data, documents, and records that were collected and studied did not exist until after the research was proposed to the IRB (the application to the JHU IRB was received by the IRB on September 26, 2003; the research publication referenced above indicates that the interventions were conducted and data collected between March 2004 and September 2005). Given this, the research does not qualify for exemption under 45 CFR 46.101(b)(4).

(e) The cover page of the Grant Application to the AHRQ indicated that the project involved non-exempt human subjects research (box "4. Human Subjects Research" was checked, "Yes").

(f) The JHU IRB Exemption Review Form for this proposal indicated that the reviewer believed that the project was human subjects research (Question "A. Does this proposal qualify as research?" was checked "Yes").

(g) A memo from the principal investigator to the Chair of the JHU-IRB X dated November 23, 2004 to request an amendment to the protocol stated, "The original application requested implementation of five interventions in over 100 intensive care units in the state of Michigan. We would like to offer one of the interventions to AscensionHealth acute care facilities….The intervention we would like to implement is the Comprehensive Unit-Based Safety Program." Similarly, an amendment dated November 11, 2005 requested the addition of 14 additional intensive care units in the state of Rhode Island. This indicates that the principal investigator believed that the intervention was part of the original research

proposal and that any change to such research interventions needed to be reviewed and approved by the JHU IRB.

(h) The above-referenced publication referred to the intervention at the Michigan hospitals as "study intervention" throughout the publication. The publication also stated, "To build on this research, we studied the extent to which these infections could be reduced in Michigan, using an intervention as part of a statewide safety initiative regarding patients in ICUs….Between March 2004 and September 2005, each ICU implemented several patient-safety interventions, according to a prospective cohort study design, and monitored the effect of these interventions on specific safety measures." This indicates that the interventions were part of a prospective research study.

(i) The above-referenced publication stated "The primary study hypothesis was that the rate of catheter-related bloodstream infection would be reduced during the first 3 months after implementation of the study intervention as compared with baseline. A secondary hypothesis was that the observed decrease in the rate of infection between 0 and 3 months after implementation of the study intervention would be sustained during the subsequent observation period." This indicates that the interventions were part of a prospective research study to test several hypotheses.

(j) A publication titled "Creating High Reliability in Health Care Organizations" published in the journal HSR: Health Services Research August of 2006 stated, regarding this project, "The project was designed as a prospective cohort study to evaluate the effects of implementing patient-safety interventions. The research was conducted from September 30, 2003 to September 30, 2005." This indicates that the interventions at the hospitals were research interventions that had been prospectively studied.

(k) Your March 30, 2007 letter stated, "The Keystone Center of The Health Trust of the Michigan Health and Hospital Association was engaged in the exempt research activity and collected de-identified data for transmission to JHU." This indicates that JHU believes that MHA was engaged in the research activity.

Based on the above information, OHRP finds that the implementation of the Comprehensive Unit-based Safety Program that included the ICU Safety

Reporting System at Michigan and Rhode Island hospitals, the subsequent collection and analysis of data from ICU patients exposed to those interventions, and the surveys of hospital personnel, represented non-exempt human subjects research that was conducted without appropriate IRB review and approval, in contravention of HHS regulations at 45 CFR 46.103(b) and 109(a). Although JHU asserts that the interventions carried out by the Michigan hospitals were not human subjects research, but quality improvement activities, OHRP notes that quality improvement activities can also be research activities. In addition, JHU failed to ensure that all collaborating institutions engaged in the research operated under an appropriate OHRP-approved assurance of compliance as required by terms of the JHU institutions' FWAs.

(2) Your March 30, 2007 letter stated, "It is JHM's interpretation that a project which is reviewed by an IRB and classified as exempt research does not require adherence to the standards for obtaining informed consent as set forth in 45 CFR 46.116. Therefore, we do not believe that there was failure to obtain effective informed consent for Dr. Pronovost's exempt research project." The above-referenced publication also stated, "Informed consent was waived because the study was considered exempt from review."

OHRP finds that, given that the project involved non-exempt human subjects research, JHU failed to ensure that the requirements for obtaining and documenting the legally effective informed consent of the subjects or the subjects' legally authorized representative under HHS regulations at 45 CFR 46.116 and 46.117 were satisfied. OHRP notes that the subjects of the research were both the healthcare providers at the participating ICUs and their patients.

Required Action: By August 31, 2007 please provide OHRP with corrective action plans to address the above findings.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Kristina C. Borror, Ph.D.
Director
Division of Compliance Oversight

cc:

Ms. Barbara L. Starklauf, Asst Dean for Human Subjects Research Compliance, JHU School of Medicine
Dr. Howard M. Lederman, IRB Chairperson/Professor, Pediatrics & Medicine, John Hopkins Hospital
Dr. Gary Briefel, Chairperson IRB #5/Assoc. Professor, Department of Medicine Nephrology, Johns Hopkins Bayview Medical Center
Dr. David R. Cornblath, IRB Chairperson/Professor, Neurology, Johns Hopkins Hospital
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