DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852

Telephone: 240-453-8132
FAX: 240-453-6909
E-mail:kristina.borror@hhs.gov

November 6, 2007

Daniel E. Ford, MD, MPH
Vice Dean for Clinical Investigation
John Hopkins University School of Medicine
733 N. Broadway
Rm#115
Baltimore, MD 21205

Janet A. DiPietro, Ph.D.
Institutional Official
Johns Hopkins Bloomberg School of Public Health
615 N. Wolfe Street
Suite E1100
Baltimore, MD 21205

Eaton E. Lattman, Ph.D.
Dean for Research
Johns Hopkins University
Office of the Dean
237 Mergenthaler Hall
Baltimore, MD 21218

RE: Human Subject 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' September 25, 2007 letter responding to OHRP's July 19, 2007 letter containing determinations of non-compliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46).

In its July 19, 2007 letter, OHRP made the following determinations regarding the research described in the above-referenced 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.

OHRP found 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). In addition, OHRP found that 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 found 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.

Corrective Action: OHRP acknowledges that JHU has instructed the principal investigator (PI) to suspend all activities related to the project until appropriate IRB review and approval is obtained at JHU, and the principal investigator has confirmed that all activity involving data collected for initiative purposes has been stopped. JHU is identifying all quality assurance/quality improvement (QA/QI) proposals for which federal funding is being sought; such proposals will be examined to determine if IRB review was conducted or if exempt status was not granted inappropriately. If these are not the case, the PIs for the proposals will be contacted and informed that prospective data collection requires IRB review and that an application for exempt status will not be accepted for these projects.

In addition, JHU will work with the Office of Research Administration to ensure compliance with the requirement to verify an OHRP-approved assurance is on file for collaborating institutions. The JHU policy on QA/QI has been revised so that faculty will be cognizant of the need for IRB review of projects that involve prospective collection of data for QA/QI purposes linked to research activity. OHRP notes, however, that this policy states, "When the purpose of an activity is to assess the success of an established program in achieving its objectives and the information gained from the evaluation will be used to provide feedback to improve that program, the activity is not human subjects research." This statement is not always true.

Required Action: By December 18, 2007 please provide OHRP with a report on the status of IRB review of this project and of the audit of other QA/QI activities.

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, Assistant 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
Dr. Richard Moore, Chairperson JHM IRB #3/Professor Department of Medicine, JHU School of Medicine
Ms. Laura E. Rocco, IRB Chairperson/Research Associate, Department of Clinical Pharmacology, The Johns Hopkins Hospital
Ms. Patricia M. German, Director, Research Subjects, Johns Hopkins School of Hygiene and Public Health
Dr. Ronald Gray, IRB Chair, IRB #1, Johns Hopkins Bloomberg School of Public Health
Dr. Jonathan Links, Chair, IRB #2, Johns Hopkins Bloomberg School of Public Health
Dr. Michael E. McCloskey, Professor, JHU
Dr. Peter Pronovost, JHU School of Medicine
Ms. Marlene Hulteen, Michigan Health & Hospital Association
Dr. Francis Chesley, Agency for Healthcare Research and Quality

Dr. Ivor Pritchard, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Ms. Shirley Hicks, OHRP
Dr. Irene Stith-Coleman, OHRP
Ms. Patricia El-Hinnawy, OHRP
Ms. Kelley Booher, OHRP
Mr. Barry Bowman, OHRP