DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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December 30, 2008

Jose R. Carlo, MD
Chancellor
University of Puerto Rico Medical Sciences Campus
P.O. Box 365067
San Juan, PR 00936-5067

RE: Human Research Protections under Federalwide Assurance FWA-5561

Dear Dr. Carlo:

Thank you for your March 7, 2008, September 11, 2008, October 1, 2008 and November 7, 2008 reports in response to our January 29, 2008 request that the University of Puerto Rico Medical Sciences Campus(UPRMSC) investigate allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46). We appreciate your investigation into the matters outlined in our request.

A. Determinations regarding your institution's system for protecting human subjects.

(1) The complainant alleged that clinical trials were being conducted without institutional review board (IRB) review and approval, in violation of HHS regulations at 45 CFR 46.103(b) and 46.109(a). Specifically, the complainant alleged that for years the UPRMSC IRB has been receiving clinical study proposals that have not been evaluated or approved, and has knowingly allowed clinical studies to be performed without IRB approval. An example of this allegedly occurred in 2005 when the residents of the Department of Orthopedic Surgery submitted 13 clinical study proposals to the IRB. The department never received responses for 11 of the proposals. The complainant alleged that, despite this, the residents performed their studies even though they were not IRB-approved.

In your March 7, 2008 report, you stated that "…no clinical trials [were] conducted by the Orthopedics Section during the period under investigation… [but] Orthopedics faculty and residents did conduct other types of research." We reviewed the report describing these projects and the report states that your institution requires that, "all project protocols must be submitted to the IRB and it is the IRB that determines their exempt status...[and] the Orthopedics Section conducted projects that had not been submitted to the IRB even though, if sent, all seven (7) would have probably been exempt."

We also reviewed the abstracts that resulted from the 2005 Orthopedics research projects and note that some of the projects included review of medical records data that did not exist when the project was proposed to the UPRMSC IRB. Such projects would not have been eligible for an exempt determination under HHS regulations at 45 CFR 46.101(b)(4) as this exemption only allows for collection of existing data—meaning the review of data already collected when the project was presented for exempt determination. We determine that non-exempt research projects (specifically, those that included plans for prospective data collection) were conducted in the Department of Orthopedic Surgery in 2005 without IRB review and approval, as required by 45 CFR 46.103(b) and 46.109(a).

Corrective Action: We acknowledge that UPRMSC IRB has conducted investigator training to ensure that investigators are knowledgeable of and comply with the HHS regulations and the exemption provisions.

(2) HHS regulations at 45 CFR 46.115(a) require that the institution prepare and maintain adequate documentation of IRB activities. The IRB files provided with your March 7, 2008 reports failed to document a complete history of protocol activities. After reviewing the study files provided for the studies outlined in the allegations, we determine that IRB protocol records in 2005 failed to include all the information stipulated at 45 CFR 46.115(a)(1) and (4) which states that "an institution, or when appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including…copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects [and] copies of all correspondence between the IRB and the investigators."

Corrective Action: We acknowledge that the UPRMSC IRB procedures have been revised to ensure that the UPRMSC IRB Office maintains copies of IRB records and research files and correspondence between the IRB and the investigators. We further

acknowledge that IRB staff received training on the regulatory requirements for IRB records.

(3) We have reviewed the June 1, 2006 Report from the Advisory Committee for the Study of IRB Committees Operation in the Medical Science Campus and the May 16th & 17th, 2007 University of Puerto Rico, School of Medicine IRB Assessment and we determine that the serious and continuing noncompliance of University of Puerto Rico IRB with HHS regulations referenced above were not reported to OHRP as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

Corrective Action: We acknowledge that the 2008 IRB procedures were revised to include processes for prompt reporting of serious and continuing noncompliance with the requirements of the HHS protection of human subjects regulations to OHRP as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

(4) The complainant alleged that the IRB lacks appropriate written IRB procedures. We reviewed the written IRB Policies and Procedures submitted with your March 7, 2008 report and determine that the written IRB procedures lacked sufficient operational details for some procedures as required by HHS regulations at 45 CFR 46.103(a) and 46.103 (b)(4) and (5); for example:

- procedures which the IRB will follow for determining which projects require review more often than annually;

- procedures which the IRB will follow for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review;

- procedures which the IRB will follow for prompt reporting to OHRP of (a) any unanticipated problems involving risks to subjects or others; (b) any serious or continuing noncompliance with 45 CFR part 46 or the requirements or determinations of the IRB; and (c) any suspension or termination of IRB approval.

Corrective Action: We acknowledge that the IRB written procedures were revised to include adequate procedural detail as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5).

(5) The complainant alleged that the IRB Chairperson and members appear to lack a detailed understanding of the specific requirements of the HHS regulations for the protection of human subjects. We acknowledge that all members of the UPRMSC IRB and IRB staff

must complete an online training and pass an examination prior to joining the IRB, and that the institution now employs the use of Collaborative IRB Training Initiative (CITI) Training Program offered by the University of Miami. IRB members are required to complete course refreshers every two years. Given this, we determine that this allegation is unproven.

B. <u>Recommendation:</u>

(1) Regarding the IRB Policies and Procedures, page 23, section 13, we recommend that more detail be added about which IRB records will be maintained in accordance with the specifications outlined in the HHS regulations found at 45 CFR 46.115(a)(1) and (4).

In addition to reviewing the corrective actions listed above, we reviewed the revised UPRMSC IRB Policies and Procedures (dated 9/1/2008), recent IRB meeting minutes, the status of the implementation of proposed modifications to the University's human research protection program. These corrective actions adequately address our determinations and are appropriate under the University of Puerto Rico's FWA.

At this time, there should be no need for further involvement by our office in this matter. Please notify us if you identify new information which might alter this determination.

We appreciate your institution's continued commitment to the protection of human research subjects.

Sincerely,

Lisa R. Buchanan, MAOM, CIP
Compliance Oversight Coordinator
Division of Compliance Oversight

cc:
Ms. Dorianne Santana, IRB administrator, University of Puerto Rico Medical Sciences Campus
Dr. Alan M. Preston, Chair, IRB #1
Dr. Margarita Irizarry, Chair, IRB #2
Dr. Luz A. Muniz, Chair, IRB #3
Dr. Joanne Less, Food and Drug Administration
Dr. Andrew C. von Eschenbach, Commissioner, U.S. Food and Drug Administration (FDA)