DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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February 12, 2003

Dr. John R. Sladek, Jr.
Vice Chancellor for Research
Campus Box A095
School of Medicine, Room 1660
Office of the Chancellor
University of Colorado Health Sciences Center
4200 East Ninth Avenue
Denver, CO 80262

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1494

Research Projects: COMIRB #93-426 and COMIRB #97-733
Principal Investigator: Carol Kruse, Ph.D.

Dear Dr. Sladek:

The Office for Human Research Protections (OHRP) has reviewed the University of Colorado's (UC) November 15, 2000 and March 12, 2001 reports submitted in response to OHRP's August 22, 2000 letter regarding the above-referenced research. OHRP apologizes for the delay in its response.

Based on the review of your report, OHRP makes the following determinations regarding the above-referenced research:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.116(a)(1) stipulate that informed consent include a statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and an identification of any procedures which are experimental. OHRP notes that your November 15, 2000 report stated the following:

> (a) "Dr. Kruse's justification for establishing this bank was her understanding that the University of Colorado Hospital surgical consent form was sufficient for research on remnant tissue and the establishment of a tissue bank, thus making it exempt from COMIRB [Colorado Medical Institutional Review Board] approval."
>
> (b) "... COMIRB finds that Dr. Kruse's establishment of this tissue bank utilizing patient identifiers is not consistent with federal regulations."
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> (c) "It is COMIRB's opinion that the dispute over informed consent and the use of identifiers was a result of Dr. Kruse's misunderstanding of the federal regulations, fostered by the practices of Surgical Pathology, shared by other colleagues and exacerbated by outdated language in the University of Colorado Hospital surgical consent form."

OHRP also notes that the informed consent document for the above-referenced research does not mention the fact that tissue samples would become part of a tissue bank. As a result, OHRP finds that the informed consent process for the above-referenced research failed to describe that tissue samples from subject's tumors were placed into a tissue bank which contained subject identifiers in contravention of HHS regulations at 45 CFR 46.116(a)(1).

Corrective Action: OHRP acknowledges that (i) UC has required that the investigator discontinue banking tissue samples using subject identifiers; (ii) the investigator must develop a specific consent form for the establishment of such a tissue bank; and (iii) the Tissue Procurement Committee at UC has rewritten the hospital consent form to ensure that it meets the requirements of the HHS regulations.

(2) HHS regulations at 45 CFR 46.103(a) and (b)(5) require prompt reporting to the institutional review board (IRB), appropriate institutional officials, the Department or Agency head and OHRP of any unanticipated problems involving risks to subjects or others. OHRP notes that UC's November 15, 2000 report states:

> (a) "... the COMIRB believes that the allegation that Dr. Kruse did not immediately inform the sponsor of problems with the biologics used for patient treatment is without merit. However, Dr. Kruse's failure to notify COMIRB in the same timely fashion is more problematic."
>
> (b) "In this case the COMIRB believes it should have been notified immediately of the initial problems with treatment biologics so a determination could have been made for continued treatment."

Based on the above statements and other material submitted with UC's November 15, 2000 report, OHRP finds that the investigator for the above-referenced research failed to report unanticipated problems involving risks to subjects or others as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

Corrective Action: OHRP acknowledges that Dr. Kruse has been counseled on the requirements of the HHS regulations regarding reporting of unanticipated problems involving risks to subjects or others.

OHRP recommends that UC consider reminding all investigators of the regulatory requirements to report unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with the HHS regulations or the IRB's requirements or determinations to the IRB, appropriate institutional officials, OHRP, and the Department of Agency head as required by HHS regulations at 45 CFR 46.103(a) and 103(b)(5).

(3) In its August 22, 2000 letter, OHRP presented an allegation that the investigator deviated from the IRB-approved protocol without obtaining IRB approval, in contravention of HHS requirements at 45 CFR 46.103(b)(4)(iii). In specific, it was alleged that a biologic used in the above-referenced research was administered by a route not approved in the protocol. OHRP finds that this allegation could not be substantiated.

(4) In its August 22, 2000 letter, OHRP presented an allegation that the investigator failed to follow procedures which minimized risks to subjects, as required by HHS regulations at 46 CFR 46.111(a)(1). In specific, it was alleged that (i) the biologic used in the above-referenced research was washed and possibly administered in unbuffered saline; (ii) the biologic for subject use was delivered to the investigator's home resulting in harm to subjects; and (iii) the investigator had inadequate laboratory standard operating procedures. OHRP finds that these allegations could not be substantiated.

OHRP finds that the corrective actions noted above adequately address the findings of noncompliance and are appropriate under the UC MPA. As a result of this determination, there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified which might alter these determinations.

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,

Patrick J. McNeilly, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Ms. Lisa Jensen, COMIRB Director
Dr. Cornelius Rietmeijer, Co-Chair, COMIRB Panel A
Mr. Ken Easterday, Co-Chair, COMIRB Panel A
Dr. Norm Stoller, Chair, Co-COMIRB Panel B
Dr. Hans Neville, Co-COMIRB Panel B
Dr. Adam Rosenberg, Co-Chair, COMIRB Panel C
Mr. David Lawellin, Co-Chair, COMIRB Panel C
Mr. Stephen Bartlett, Chair, COMIRB Panel D
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