DEPARTMENT OF HEALTH & HUMAN SERVICES

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

Dear Mr. Gershen, Ms. Cashman, Dr. Beister, Dr. Hiatt, Dr. Gabow, and Dr. Thorsland:

The Office for Human Research Protections (OHRP) has reviewed your report of February 27, 2001 regarding the human subjects research conducted at the University of Colorado Health Sciences Center (CU).

Based upon its review, OHRP makes the following determinations:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.305(a) require that the Institutional Review Board (IRB) make seven specific findings when reviewing and approving research proposing the involvement of prisoners as subjects. Furthermore, HHS regulations at 45 CFR 46.305(c) and 46.306(a)(1) require that institutions conducting HHS-supported research involving prisoners as subjects certify to the Secretary of Health and Human Services that the IRB has made these seven findings.

OHRP finds that CU failed to certify to OPRR or OHRP, acting on behalf of the Secretary of Health and Human Services, (or to any other HHS office or official) that the IRB fulfilled it duties stipulated under 45.305(a) for HHS-supported research projects involving prisoners as subjects as required by HHS regulations at 45 CFR 46.305(c) and 46.306(a)(1).

Corrective Action: OHRP acknowledges CU's plan to correct this immediately and to report all HHS-supported research involving prisoners to OHRP.

(2) OHRP finds that the IRB approved research contingent upon substantive modifications or clarifications without requiring additional review by the convened IRB (Protocol # 97-722). OHRP recommends the following guidelines in such cases: (a) When the convened IRB requests substantive clarifications, protocol modifications, or informed consent document revisions, IRB approval of the proposed research must be **deferred**, pending subsequent review by the convened IRB of responsive material. (b) Only when the convened IRB stipulates specific revisions requiring simple concurrence by the investigator may the IRB Chair or another IRB member designated by the Chair subsequently approve the revised research protocol on behalf of the IRB under an expedited review procedure.

Required Action: OHRP acknowledges that CU has since instituted bimonthly meetings of the Colorado Multiple IRB (COMIRB). By May 31, 2001 please provide a plan that includes additional actions that CU will take to ensure that the COMIRB will approve research contingent upon substantive modifications or clarifications only after additional review by the convened IRB.

(3) HHS regulations at 45 CFR 46.111(a)(1) and (a)(2) require that, in order to approve research, the IRB shall determine that risks to subjects are minimized and that risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In making these determination, the IRB must carefully assess the level of risk associated with the proposed research.

OHRP concurs with CU's finding that protocol number 99-018 ("Pharmacokinetics and tolerability of hydroxyurea in HIV-infected children") should not have been designated as involving "no greater than minimal risk."

Corrective Action: OHRP acknowledges that this protocol was deferred by the COMIRB and has been withdrawn from consideration by the investigator. OHRP also notes that COMIRB now has detailed risk assessment guidelines for its members. OHRP finds that these corrective actions are adequate to address this finding.

(4) OHRP finds that at least one IRB meeting (February 2, 2000) involved voting irregularities where a member and her alternate both voted on several protocols.

Corrective Action: OHRP acknowledges that COMIRB now has standard operating procedures on counting votes of members and alternates that is used in training staff. OHRP finds that these corrective actions are adequate to address this finding.

At this time, OHRP provides the following additional guidance.

(5) OHRP recommends that updated IRB rosters be provided to OHRP as changes are made.

(6) OHRP recommends that the CU checklist of "Special Questions for Research Involving Prisoners" note that HHS-supported research in category (C) (research on conditions particularly affecting prisoners as a class) and some in category (D) (research involving control groups which may not benefit from the research) of HHS regulations 45 CFR 46.306(a)(2) may proceed only after the Secretary has consulted with appropriate experts and published notice, in the Federal Register, of his intent to approve such research.

(7) CU forms "Special Questions for Research Involving Pregnant Women" and "Special Questions for Research on Fetuses" appear to be missing an important alternate basis for approval from HHS regulations at 45 CFR 46.207 and 208: the purpose of the activity is to meet the health needs of the mother (or the particular fetus). OHRP recommends that the this alternative be added to the checklists.

Please submit to OHRP your response to finding (2) no later than June 20, 2001. If upon further review of the concerns and questions, CU identifies additional instances of non-compliance with the HHS regulations for protection of human subjects, please include detailed corrective action plans to address the noncompliance.

OHRP appreciates your institution's continued commitment to the protection of human research subjects. Do not hesitate to contact me if you have any questions regarding this matter.

Sincerely,

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

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