DEPARTMENT OF HEALTH & HUMAN SERVICES

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

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

The Office for Human Research Protections (OHRP) has reviewed the University of Colorado Health Sciences Center's (CU's) reports dated September 27, 1999, January 14, 2000, February 14, 2000, May 15, 2000, February 27, 2001, and May 17, 2001. OHRP has determined that the corrective actions summarized below appropriately address the issues raised:

(1) OHRP found that CU failed to certify to OPRR or OHRP, acting on behalf of the Secretary of Health and Human Services (HHS), (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 found that the IRB approved research contingent upon substantive modifications or clarifications without requiring additional review by the convened IRB (Protocol # 97-722).

Corrective Action: OHRP acknowledges that CU has since instituted bimonthly meetings of the Colorado Multiple IRB (COMIRB). In addition, the COMIRB has put into place a Standard Operating Procedure to help ensure, among other things, that the IRB 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. OHRP concurred 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Corrective Action: OHRP acknowledges that this protocol was deferred by the COMIRB and has been withdrawn from consideration by the investigator.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.

(4) OHRP found 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.

(5) OHRP found that continuing review of research by the IRB regularly failed to be timely, substantive and meaningful.

Corrective Actions: OHRP acknowledges that CU has implemented several IRB personnel and management changes, including the creation of multiple IRBs and the implementation of substantial information management upgrades, to help facilitate

meaningful continuing review. In addition, COMIRB's Policies and Procedures outline appropriate mechanisms for continuing review.

(6) HHS regulations at 45 CFR 46.110(b)(1) limit the use of expedited review procedures to specific research categories published in the Federal Register at 63 FR 60364. OHRP found that COMIRB failed to follow these procedures for expedited review.

Corrective Action: COMIRB's new Policies and Procedures outline appropriate mechanisms for conducting and reporting expedited review.

(7) OHRP found that the institution did not have written IRB policies and procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(b)(4) and (5).

Corrective Action: COMIRB's new Policies and Procedures are in compliance with the regulations.

(8) OHRP found that IRB protocol records failed to include all the information stipulated at HHS regulations at 45 CFR 46.115(a)(1),(3),(4), and (7) and IRB minutes including at the information stipulated at 45 CFR 46.115(a)(2).

Corrective Action: COMIRB's new Policies and Procedures help ensure that the IRB minutes are in compliance with HHS regulations.

(9) OHRP found that CU failed to provide the COMIRB with adequate resources and sufficient staff to support the IRB's activities, as required by HHS regulations at 45 CFR 46.103(b)(2).

Corrective Action: CU has taken appropriate actions to ensure that the COMIRB has adequate resources and sufficient staff to support the IRB's review and recordkeeping duties.

(10) HHS regulations at 45 CFR 46.404-407 require specific findings on the part of the IRB for approval of research involving children. OHRP's review of IRB documents revealed no evidence that the IRB consistently made the required findings when reviewing research involving children.

Corrective Action: COMIRB's new Policies and Procedures outline appropriate mechanisms for conducting and reporting review and approval of research involving children.

As a result of the above corrective actions, 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 this determination.

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.
Compliance Oversight Coordinator
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