DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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August 19, 2002

Mary Ellen Sheridan, Ph.D.
Associate Vice President for Research
University of Chicago
University Research Administration
970 East 58th Street
Chicago, IL 60637

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1264

Research Project: **Controlled Trial of Intermittent Pamidronate Use in Childhood Osteoporosis Associated with Cerebral Palsy**
Protocol Number: **10218**
Principal Investigator: Dr. C. Egla Rabinovich

Dear Dr. Sheridan:

The Office for Human Research Protections (OHRP) has reviewed the University of Chicago's (UC) June 26, 2002 report which was submitted in response to OHRP's letters of April 23, 2002 and May 13, 2002.

Based on its review, OHRP makes the following determinations:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.111(a)(1) require that in order to approve research covered by the regulations, the Institutional Review Board (IRB) shall determine that the risks to the subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk. In its April 23, 2002 letter, OHRP found that the UC IRB failed to ensure that this requirement was satisfied for the above-referenced research.

Corrective Action: OHRP acknowledges that UC has (i) retrained its IRB staff and IRB chairs on the process for summarizing the concerns of the IRB and assuring that investigators have responded to all issues raised by the IRB; and (ii) developed a reviewer's checklist to ensure that the requirements for approval of research involving children are addressed by the IRB. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the UC MPA.

(2) HHS regulations at 45 CFR 46.116(a)(2) require that informed consent include a complete description of any reasonably foreseeable risks or discomforts to the subject. In its April 23, 2002 letter, OHRP found that the informed consent document for the above-referenced research failed to include a description of all the reasonably foreseeable risks associated with electrolyte imbalances associated with the administration of pamidronate.

Corrective Action: OHRP acknowledges that UC has revised its IRB policy and procedure manual to require that investigators submit the investigators' brochure or the package insert for a study agent to assist in assessing the reasonably foreseeable risks in such studies. In addition, UC will recommend to investigators that they consider the risks of a protocol from the subject's viewpoint and include in the informed consent process all the information necessary for a subject to make an informed decision about whether or not to participate. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the UC MPA.

(3) HHS regulations at 45 CFR 46.116 require that information that is given to a subject must be in language understandable to the subject or the subject's legally authorized representative. In its April 23, 2002 letter, OHRP found that the language of the IRB-approved informed consent document for the above-referenced research contained complex language that may not have been understandable to many potential subjects or their legally authorized representatives.

Corrective action: OHRP acknowledges that UC agrees that informed consent documents should be in lay language and has procedures in place to ensure that consent forms are understandable. OHRP finds that this corrective action adequately addresses the above finding and is appropriate under the UC MPA.

(4) In its April 23, 2002 letter, OHRP found that UC did not have written IRB policies and procedures that adequately describe certain activities, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5).

Corrective Action: OHRP acknowledges that UC has provided updated written procedures for its Biomedical IRB, as well as for the Social Service Administration/Chapin Hall IRB. OHRP finds that this corrective action adequately addresses the above finding and is appropriate under the UC MPA.

(5) HHS regulations at 45 CFR 46.115(a)(2) require that minutes of IRB meetings provide a written summary of the discussion of controverted issues and their resolution. In its April 23, 2002 letter, OHRP found that tape recording of UC IRB meetings did not fulfill these requirements.

Corrective Action: OHRP acknowledges that UC has amended its MPA to require written minutes of IRB meetings. OHRP finds that this corrective action adequately addresses the above finding and is appropriate under the UC MPA.

As a result of these determinations, 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.

At this time, OHRP would like to provide the following additional guidance:

(6) OHRP notes that the Policy and Procedure for Adverse Events provided with your June 26, 2002 report defines an "adverse event" as "... an undesirable and unintended, although not necessarily unexpected, result of therapy or other intervention." The policy also states that investigators are required to report adverse events that are either serious or unexpected. HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5)(i) require that institutions have written procedures for prompt reporting to the IRB, appropriate institutional officials, the Department or Agency head and OHRP of any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with the HHS regulations or the requirements or determinations of the IRB. OHRP would like to remind UC that unanticipated problems involving risks to subjects or others may include situations that are unrelated to an "adverse event" as defined in the UC policy. OHRP recommends that UC review its procedures to ensure that investigators have a clear understanding of what must be reported to the IRB and other officials.

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: Dr. Jonathan Moss, UC
Dr. Tina Rzepnicki, UC

Dr. Bennett Bertenthal, UC
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Greg Koski, OHRP
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