DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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April 23, 2002

Mary Ellen Sheridan, Ph.D.
Associate Vice President for Research
University of Chicago
University Research Administration
970 East 5th 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's) February 21, 2002 report regarding the above-referenced research. Based on the documents provided in your report and subsequent discussion during a telephone call with you on March 6, 2002, OHRP makes the following determinations regarding the above-referenced research:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.111(a)(1) require that in order to approve research 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. OHRP finds that the UC IRB failed to ensure that this requirement was satisfied for the above-referenced research. In specific, OHRP notes the following:

(a) The IRB-approved protocol for the above-referenced research stated "Serum calcium, phosphate, creatinine, potassium and magnesium will be measured 12 hours after each dose. Subjects will be asked to return to the CRC [Clinical Research Center] as an outpatient two weeks after therapy for repeat measures of markers of bone metabolism along with repeat serum calcium, phosphate, creatinine, potassium and magnesium."

(b) During its meeting of December 7, 1999 an IRB member noted that the delay in hypocalcemia in patients receiving pamidronate may be 3-4 days and that the monitoring schedule in the protocol may not be adequate. The IRB member also noted that many patients receiving pamidronate develop symptomatic hypocalcemia.

(c) The December 21, 1999 letter from the IRB chair to the investigator failed to relay the concern of the IRB regarding adequacy of monitoring calcium levels after pamidronate administration.

(d) The protocol received full IRB approval on January 17, 2000.

(e) A subject was admitted to the CRC on September 11, 2001 and received the three daily doses of pamidronate, including a final dose on September 13, 2001 at 4:30 p.m. and serum calcium levels were monitored on September 14, 2001 at 8:30 a.m. OHRP notes that serum calcium levels decreased from 10.4 mg/dl on September 11, 2001 to 9.2 mg/dl on September 14, 2001.

(f) The subject was discharged home on September 14, 2001 at 11:15 a.m. and died at approximately 4:00 p.m. the same day.

OHRP notes that an autopsy failed to identify a cause of death.

Corrective Action: OHRP acknowledges the corrective actions taken by UC to address the above finding including (i) retraining IRB staff and IRB chairs on the process for summarizing and assuring that investigators have responded to all issues raised by the IRB; and (ii) the development of a reviewer's checklist of assure that the requirements for approval of research involving children are addressed by the IRB. OHRP finds these corrective actions to be satisfactory and appropriate under the UC MPA.

(2) HHS regulations at 45 CFR 46.116(a)(2) require that informed consent include a complete description of the reasonably foreseeable risks or discomforts to the subject. OHRP finds 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. Although the informed consent document

stated, "Body chemistry values can become abnormal, although usually not to where it can cause illness," there is no description as to the reasonably foreseeable consequences of such abnormalities, such as tetany, laryngospasm, seizure, and cardiac arrhythmia from hypocalcemia, as well as hypotension and cardiac disturbances from hypokalemia.

(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 their legally authorized representative. OHRP finds 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. OHRP notes that the UC IRB required changes to the informed consent document to make it more understandable and has acknowledged that certain statements in the informed consent document remained complex.

Required Action 1: By May 31, 2002, UC must submit to OHRP a satisfactory corrective action plan to address findings (2) and (3) above.

(4) OHRP finds that the institution does not have written IRB policies and procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5):

(a) The UC Biomedical IRB lacks written procedures for determining which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review as required by HHS regulations at 45 CFR 46.103(b)(4)(ii).

(b) The UC Biomedical IRB lacks written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, the Department or Agency head, and OHRP of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance; and (ii) any suspension or termination of IRB approval as required by HHS regulations at 45 CFR 46. 103(a) and (b)(5).

(c) The Social Service Administration (SSA)/Chapin Hall IRB does not currently have written operating procedures.

Corrective Action: It is OHRP's understanding that the structure of the system for the protection of human subjects at UC is currently undergoing changes which include the expansion of the number of IRBs which review biomedical research and the restructuring of the SSA/Chapin Hall and Social and Behavioral Science (SBS) IRBs. OHRP acknowledges that UC is currently working to develop written procedures for the SSA/Chapin Hall IRB.

Required Action 2: By May 31, 2002, UC must submit to OHRP revised written procedures

for both the Biomedical and SSA/Chapin Hall IRBs that adequately address the deficiencies noted above. In order to assist UC in revising its IRB policies and procedures, please see the enclosed Guidance for Formulating Written IRB Policies and Procedures.

(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. OHRP notes that the UC MPA provides for the use of written summary or a tape recording of the discussion of controverted issues and their resolution. OHRP finds that a tape recording of IRB minutes does not fulfill the requirements of HHS regulations at 45 CFR 46.115(a)(2).

Required Action 3: By May 31, 2002, UC must submit to OHRP an amendment to its MPA addressing the above finding.

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

(6) Where HHS regulations require specific findings on the part of the IRB, such as (a) approving a procedure which alters or waives the requirements for informed consent [see 45 CFR 46.116(d)]; (b) approving a procedure which waives the requirement for obtaining a signed consent form [see 45 CFR 46.117(c)]; (c) approving research involving prisoners (see 45 CFR 46.305-306); or (d) approving research involving children (see 45 CFR 46.404-407), the IRB should document such findings. OHRP strongly recommends that all required findings be fully documented in the IRB minutes, including protocol-specific information justifying each IRB finding.

(7) IRBs must determine which protocols require continuing review more often than annually, as appropriate to the degree of risk [see 45 CFR 46.103(b)(4) and 46.109(e)]. OHRP recommends that the minutes of IRB meetings clearly reflect these determinations regarding risk and approval period (review interval).

(8) OHRP notes that the protocol coversheet for the SSA/Chapin Hall IRB as well as the protocol forms for the SBS IRB provide a checklist for categories of research eligible for expedited review. OHRP would like to point out that certain of the categories of research eligible for expedited review contain additional stipulations which are not included on the protocol coversheet (please see http://ohrp.osophs.dhhs.gov/humansubjects/guidance/expedited98.htm). For example, expedited review may be appropriate for the collection of blood samples by finger stick, heel stick, ear stick or venipuncture as follows:

(a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently then 2 times per week; or

(b) from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

(9) In conducting continuing review of research not eligible for expedited review, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research, including (a) the number of subjects accrued; (b) a description of any adverse events or unanticipated problems involving risks to subjects or others and of any withdrawal of subjects from the research or complaints about the research; (c) a summary of any recent literature, findings obtained thus far, amendments or modifications to the research since the last review, reports on multi-center trials and any other relevant information, especially information about risks associated with the research; and (d) a copy of the current informed consent document. Primary reviewer systems may be employed, so long as the full IRB receives the above information. Primary reviewers should also receive a copy of the complete protocol including any modifications previously approved by the IRB (see OPRR Reports 95-01). Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

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

Enclosure: OHRP Guidance on Written IRB Procedures

cc: Dr. Paula K. Jaudes, President and CEO, La Rabida Children's Hospital
Mr. Edward Cucci, President, Louis A. Weiss Memorial Hospital
Dr. Jonathan Moss, UC
Dr. John Craig, UC
Dr. John Bartot, UC
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Greg Koski, OHRP

Dr. Melody Lin, OHRP
Dr. Michael A. Carome, OHRP
Mr. George Gasparis, OHRP
Dr. Jeffrey Cohen, OHRP
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Mr. Barry Bowman, OHRP