DEPARTMENT OF HEALTH & HUMAN SERVICES

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January 22, 2001

Raelene Rathbone, M.D., Ph.D.
Associate Dean, Research (Health Sciences)
McMaster University
Faculty of Health Sciences
1200 Main Street W., Room 3E5C
Hamilton, Ontario L8N 3Z5, Canada

RE: Human Research Subject Protections Under Cooperative Project Assurance (CPA) T-4243

Research Projects: Pediatric Oncology Group (POG) protocols
Principal Investigator: Ronald Barr, M.D.

Dear Dr. Rathbone:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed the McMaster University's (MU's) reports dated November 15, 1999 and January 31, 2000 regarding noncompliance with Department of Health and Human Services (HHS) regulations for protection of human subjects (45 CFR Part 46) involving the above referenced research. OHRP apologizes for the delay in its response

Based upon its review of the materials submitted with your reports, OHRP finds that the MU has adequately addressed the issues set forth in OPRR's letter of July 13, 1999 and appears to be in compliance with the requirements of HHS regulations for the protection of human subjects at 45 CFR Part 46.

In particular, OHRP notes the following efforts made by MU:

(1) Development of updated Institutional Review Board (IRB) policies and procedures.

(2) Consolidation and cross referencing of IRB records.

(3) Incorporation of changes to POG informed consent documents including:

(a) Specific statements referencing appropriate alternative procedures or courses of treatment.

(b) Statements regarding (i) termination by the investigator, (ii) consequences of withdrawal from the study, and (iii) conveyance of new findings to subjects.

(4) Documentation of all IRB actions in minutes of IRB meetings.

(5) Development of procedures to ensure that all IRB-approved research undergoes continuing review on an annual basis.

As a result of the above 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 this determination.

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

(1) The MU IRB policies and procedures should be expanded to include operational details for the following procedures, in accordance with HHS regulations at 45 CFR 46.103(b)(4) and (5) which require written IRB policies and procedures describing:

(a) The procedures which the IRB will follow for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review

(b) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and Department or Agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval.

(2) HHS regulations at 45 CFR 46.115(a)(2) require that the minutes of IRB meetings document the vote on all IRB actions including the number of members voting for, against, and abstaining. OHRP strongly recommends that votes be recorded in the minutes of IRB meetings using the following format: Total = 15; Vote: For-14, Opposed-0, Abstained-1 (NAME). Simply recording votes as "unanimous" is not sufficient.

(3) Continuing IRB review of research must be substantive and meaningful. 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 at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/hsdc95-01.htm). Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

When conducting research under an expedited review procedure, the IRB Chair (or designated IRB member(s)) should receive and review all of the above referenced documentation.

(4) It appears that the MU IRB approves research contingent upon substantive modifications or clarifications without requiring additional review by the convened IRB. 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.

(5) HHS regulations at 45 CFR 46.116 require that the information provided in the informed consent documents be in language understandable to the subject.

(a) It appears that the revised POG informed consent documents approved by the IRB include complex language that may not be understandable to the parents of all subjects. OHRP recommends that MU review the POG informed consent document to ensure that language contained therein is understandable to the parents of all subjects enrolling in POG protocols.

(b) Where informed consent is documented in accordance with HHS regulations at 45 CFR 46.117(b)(1), the written informed consent document should embody, in language understandable to the subject, all the elements necessary for legally effective informed consent. Subjects who do not speak English should be presented with an informed consent document written in a language understandable to them. OHRP strongly encourages the use of this procedure whenever possible.

(6) OHRP recommends that IRBs affix the approval and expiration dates to all approved informed consent documents and stipulate that copies of these dated documents must be used in obtaining consent. This procedure helps ensure that only the current, IRB-approved informed consent documents are presented to subjects and serves as a reminder to the investigators of the need for continuing review.

The approval date should be the most recent of the following: (a) date the protocol and informed consent document were initially reviewed and approved by the IRB; (b) date of the most recent IRB continuing review and approval of the protocol and informed consent document; or (c) date that the IRB approved the most recent modification to the informed consent document. In all three circumstances, the approval date which appears on the consent document is the date of approval of the most recent version of the consent document. The expiration date should correspond to the end of the current IRB approval period.

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. Peter McCulloch, Research Ethics Board Chair, MU
Dr. William Orovan, MU
Dr. Ronald Barr, MU
Ms. Jeanette Tomaszewski, CTMB, CTEP, NCI
Commissioner, FDA
Dr. David Lepay, FDA
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