DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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January 12, 2001

Linda Latta, R.N., Ph.D.
Associate Administrator
Mary Bridge Children's Hospital & Health Center
317 Martin Luther King Jr. Way
P.O. Box 5299
Tacoma, WA 98415-0299

Edward I. Walkley, M.D.
Medical Director
Mary Bridge Children's Hospital and Health Center
317 Martin Luther King Jr. Way
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Tacoma, WA 98415-0299

RE: Human Research Subject Protections Under Cooperative Project Assurance (CPA) T-4160

Research Project: CCG-1952: Randomized Comparisons of Oral Mercaptopurine vs. Oral Thioguanine and Intrathecal Methotrexate vs. Intrathecal Methotrexate/Cytarabine/Hydrocortisone for Standard Risk Acute Lymphoblastic Leukemia
Protocol Number: 96-30
Principal Investigator: Daniel J. Niebrugge, M.D.

Dear Dr. Latta and Dr. Walkley:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed MultiCare Health System's (MultiCare's) September 7, 1999 report submitted by Dr. Richard Shine and Dr. Gordon Klatt, as well as your September 23, 1999 letter, regarding the above referenced research. OHRP apologizes for the delay in its response.

Based upon its review MultiCare's report, OHRP makes the following determinations regarding the above referenced research:

(1) OHRP finds that the above referenced research was reviewed and approved by the MultiCare Institutional Review Board (IRB) prior to enrollment of subjects, in accordance with the requirements of Department of Health and Human Services (HHS) regulations at 45 CFR 46.109.

(2) OHRP acknowledges MultiCare's finding that consent for one subject enrolled in the research was mistakenly documented with an informed consent document which was not approved by the MultiCare IRB, in contravention of the requirements of HHS regulations at 45 CFR 46.117(a).

Corrective Actions: OHRP acknowledges that the MultiCare IRB has (i)required that the investigator send a copy of every completed consent form for every subject enrolled on a Children's Cancer Group (CCG) study to the IRB; (ii) required that all non-IRB approved consent forms be removed from the file documents for all CCG protocols; and (iii) counseled the investigator who used the non-IRB approved consent form. OHRP has determined that these corrective actions adequately address the above noncompliance and are appropriate under the Mary Bridge Children's Hospital and Health Center CPA.

(3) OHRP acknowledges MultiCare's finding that modifications to the research were implemented without the review and approval of the MultiCare IRB, in contravention of the requirements of HHS regulations at 45 CFR 46.103(b)(4)(iii).

Corrective Actions: OHRP acknowledges that MultiCare has (i) executed a cooperative amendment with Children's Hospital and Regional Medical Center in Seattle for review of CCG protocols; (ii) suspended all CCG protocols until all protocols and protocol amendments have been reviewed by the IRB to assure that all protocol revisions have been reviewed and approved. OHRP has determined that these corrective actions adequately address the above noncompliance and are appropriate under the Mary Bridge Children's Hospital and Health Center CPA.

(4) HHS regulations at 45 CFR 46.116 prohibit any exculpatory language in informed consent through which the subject is made to waive, or appear to waive, any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence. OHRP finds the following language in the IRB-approved informed consent documents to be exculpatory:

> "I now voluntarily agree to have my child participate in this research study, and assume the risk for harmful results, releasing my physician and his or her associates, hospital or clinic and its personnel from liability for my child's participation."

Required Action: Mary Bridge Children's Hospital and Health Center must submit to OHRP by February 23, 2001, a satisfactory corrective action plan to ensure that all IRB-

approved informed consent documents for HHS-supported research do not include any exculpatory language.

OHRP has the following additional concerns and questions regarding the above referenced research:

(1) HHS regulations at 45 CFR 46.116 require that the information provided in the informed consent documents be in language understandable to the subject. OHRP is concerned that the informed consent document approved by the IRB for the research appeared to include complex language that would not be understandable to all parents. Please respond.

(2) OHRP is concerned that the informed consent documents reviewed and approved by the IRB failed to include the following elements required by HHS regulations at 45 CFR 46.116 (a):

(a) Section 46.116(a)(2): An adequate description of the reasonably foreseeable risks and discomforts (i.e., the risks and discomforts of intrathecal chemotherapy; in particular, the increased risk of arachnoiditis and ascending leukoencephalopathy).

(b) Section 46.116(a)(4): A description of appropriate alternative procedures or courses of treatment that might be advantageous to the subject (e.g., a description of the current standard treatments for acute lymphoblastic leukemia, and an explanation about whether the parents could select one of the treatment arms described in the protocol instead of being randomized to a treatment arm).

(c) Section 46.116(a)(7): An explanation of whom to contact in the event of a research-related injury to the subject.

(3) OHRP is concerned that the content of the boilerplate Drug Information Sheets in the informed consent documents is difficult to understand, contains information that may be irrelevant for certain research and for certain groups of subjects (e.g., children), and lacks information that may be pertinent for certain types of research (e.g., the risks of intrathecal use of the drugs). Please respond. OHRP strongly recommends that the MultiCare IRB reassess this practice.

OHRP has the following additional concerns, questions, and guidance regarding Mary Bridge Children's Hospital and Health Center's system for protecting human subjects:

(4) OHRP is concerned that the IRB may not be requesting from investigators sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. For example, the IRB appears to receive and review only

minimal information regarding (a) subject recruitment and enrollment procedures; (b) the equitable selection of subjects; and (c) provisions to protect the privacy of subjects and maintain the confidentiality of data.

(5) 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.

OHRP is concerned that continuing review of research by the MultiCare IRB regularly fails to satisfy these requirements. In specific, it appears that (i) the abbreviated continuing review progress report solicits insufficient information from investigators; (ii) continuing review progress reports are not distributed to all IRB members for review prior to IRB meetings; (iii) no IRB member receives and review a copy of the complete protocol including any modifications previously approved by the IRB during the continuing review process; and (iv) the minutes of MultiCare IRB meetings fail to document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

Please respond.

(6) HHS regulations at 45 CFR 46.115(a)(2) require that minutes of IRB meetings a written summary of the discussion of controverted issues and their resolution. OHRP is concerned that the minutes of MultiCare IRB meetings do not appear to document such discussions. Please respond.

(7) HHS regulations at 45 CFR 46.404-407 require specific findings on the part of the IRB for approval of research involving children. OHRP is concerned that the IRB documents provided with MultiCare's report appear to reveal no evidence that the IRB makes the required findings when reviewing research involving children. Please respond.

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.

(8) OHRP requires that each local IRB receive and review a copy of the NIH-approved sample informed consent document and the full NIH-approved protocol as a condition for review and approval of the local informed consent document. Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator, approved by the IRB, and reflected in the IRB minutes (see OPRR Reports 93-01 at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/hsdc93-01.htm).

(9) OHRP is concerned that Mary Bridge Children's Hospital and Health Center does not have adequate written IRB policies and procedures that describe the following activities, as required by HHS regulations at 45 CFR 46.103(b)(4) and (5):

(a) The procedures which the IRB will follow for conducting its continuing review of research.

(b) The procedures which the IRB will follow for reporting its findings and actions to the institution.

(c) The procedures which the IRB will follow for determining which projects require review more often than annually.

(d) The procedures which the IRB will follow for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review.

(e) The procedures which the IRB will follow for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been

given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

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

(10) Regarding the MultiCare IRB Policy and Procedures, please note the following:

(a) Section 8.2: The definition of a quorum should be revised to indicate that a majority of the IRB members (more than 50%) must be present, including at least one member whose primary concerns are in nonscientific areas, in accordance with the requirements of HHS regulations at 45 CFR 46.108(b).

(b) Section 8.3: Please note that HHS regulations at 45 CFR 46.107(e) stipulate that no IRB member may have a member participate in the IRB's initial or continuing of any project in which the member has a conflicting interest, except to provide information requested by the IRB. OHRP is concerned that section 8.3 is not consistent with this requirement.

(11) HHS regulations at 45 CFR 46.116(a)(8) stipulate that subjects may discontinue participation in research at anytime. The following language in paragraph 10 of the STANDARD STATEMENTS CONSENT FORM does not appear to comply with this requirement:

"In the event that I do withdraw from the study, I will continue to be followed and clinical data will continue to be collected from my medical record"

Please respond.

Please submit to OHRP your response to the above questions and concerns no later than February 23, 2001. Please provide the following in your response:

(1) A description of any corrective actions that have been or will be taken in response to any additional noncompliance identified during your evaluation of the above concerns.

(2) A copy of revised written IRB policies and procedures and IRB forms and application materials for investigators. To assist you in revising the written IRB policies and procedures, please refer to the enclosed Guidance for Formulating Written IRB Policies and Procedures.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me if you have any questions.

Sincerely,

Inese Z. Beitins, M.D.
Compliance Coordinator
Division of Compliance Oversight

Michael A.Carome,M.D.
Director
Division of Compliance Oversight

Enclosure: Guidance for Formulating Written IRB Policies and Procedures

cc: Dr. Richard Shine, Co-Chair, IRB, MultiCare
Dr. Gordon Klatt, Co-Chair, IRB, MultiCare
Dr. Daniel J. Niebrugge, Mary Bridge Children's Hospital and Health Center
Ms. Michelle Carter, IRB Secretary, MultiCare
Ms. Joan Mauer, CTEP, NCI
Dr. Greg Koski, OHRP
Dr. Melody Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Jeffrey Cohen, OHRP
Ms. Helen Gordon, OHRP
Dr. Kamal Mittal, OHRP
Mr. Barry Bowman, OHRP