DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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June 1, 2001

Enrique Beckman, M.D., Ph.D.
Chairman of the Board of Directors
Michael Reese Hospital
2816 S. Ellis Ave., Room. 753
Chicago, IL 60616

William A. Clark, Ph.D.
Executive Director
Research and Education Foundation and Research Director
Michael Reese Hospital IRB
2816 S. Ellis Ave., Room. 753
Chicago, IL 60616

RE: Human Research Subject Protections Under the Multiple Project Assurance (MPA) M-1014

Dear Dr. Beckman and Dr. Clark:

The Office for Human Research Protections (OHRP), formerly known as the Office for Protection from Research Risks (OPRR), has reviewed Michael Reese Hospital's (MRH's) letter of November 24,1999 regarding the Southwest Oncology Group (SWOG) Clinical Trials audit of June 15, 1999 and the National Surgical Adjuvant Breast and Bowel Project (NSABP) Final Audit Report transmitted to OHRP on December 7, 2000. OHRP apologizes for the delay in its response.

Based upon this review OHRP makes the following determinations relative to MRH's system for the protection of human subjects in research:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk and not less than once per year. The regulations make no provision

for any grace period extending the conduct of the research beyond the expiration date of Institutional Review Board (IRB) approval. If the IRB does not re-approve the research by the specified expiration date, subject accrual should be suspended pending re-approval of the research by the IRB. OHRP finds that the MRH IRB failed to conduct continuing review on at least an annual basis for protocols 930511 and 950802.

(2) Continuing IRB review is required as long as individually identifiable follow-up data are collected on subjects enrolled in human subjects research. This remains the case even after a protocol has been closed at all sites and protocol-related treatment has been completed for all subjects.

OHRP notes that the November 24, 1999 report submitted by MRH indicated that the MRH IRB suspended enrollment of subjects on the protocols cited in the SWOG report and conducted an audit of these protocols. Additionally, your report indicated that steps would be taken to redefine the IRB policies regarding notification of principal investigators of impending expiration dates and strict termination of studies which are not renewed in a timely fashion.

Although MRH has made these efforts to correct the noncompliance relating to continuing review of research, OHRP continues to have serious concerns about the extent to which MRH has reviewed the research approved by its IRB. Please note that OHRP has reviewed an NSABP audit report for MRH dated December 7, 2000 (copy enclosed) which identified twenty three protocols which lacked current IRB approval. This report indicated that certain protocols had not been reviewed since June 1998 and one study (protocol # NSABP-B-14) had no records available on site.

Action 1 - Required: The MRH, in conjunction with all of its investigators and clinical practitioners, as well as relevant administrators, must conduct an adequate audit of all its ongoing research projects to ensure that they have undergone appropriate continuing review as required by HHS regulations at 45 CFR 46.109(e). MRH must suspend immediately any Federally sponsored research involving human subjects that has not undergone appropriate continuing review by the MRH IRB. For any project affected by this suspension, enrollment of new subjects must cease immediately except in extraordinary cases approved in advance by OHRP (OHRP would expect requests for approval of such cases to be rare). Furthermore, research activities involving previously enrolled subjects should continue only where the IRB finds that it is in the best interests of individual subjects to do so. For each affected protocol this suspension must remain in effect until the protocol has undergone appropriate continuing review by the IRB. Additionally, by July 15, 2001 MRH must provide OHRP with a report on the results of this audit and a list of any research activities that have been suspended as a result of this audit.

(3) HHS regulations at 45 CFR 46.103(b)(iii) require that proposed changes in approved research be promptly reported to the IRB and that the IRB ensure that such proposed changes not be initiated without review and approval except when necessary to eliminate apparent immediate hazards to the subject.

The report submitted by MRH indicated that certain amendments to protocols 920205, 940408, and 950802 were either not reviewed by the IRB or could not be located in the IRB or principal investigator's files. OHRP finds that changes in human subject research were conducted without IRB review and approval.

Action 2 - Required: By July 15, 2001, MRH must submit to OHRP a satisfactory corrective action plan to ensure that all protocol amendments are reviewed by the IRB prior to their initiation, as required by 45 CFR 46.103(b)(iii).

(4) OHRP finds that MRH 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 procedures which the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) 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; and (iii) 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.
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> (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.

Action 3 - Required: By May 31, 2001, MRH must submit to OHRP revised written IRB policies and procedures that adequately describe the operational details of all activities stipulated by HHS regulations at 45 CFR 46. 103(a) and 46.103(b)(4) and (5).

OHRP has the following questions, concerns, and guidance:

(5) OHRP records indicate that the MRH MPA was due to expire on February 28, 1999. Additionally, MRH was sent a letter by Diane L. Aiken of OPRR on April 20,1999 which stated, "As you know, your MPA expired on February 28,1999 and has been

administratively extended by OPRR. A new assurance must be submitted to and approved by OPRR as quickly as possible." Please contact OHRP's Division of Policy and Assurance (Ms. Roslyn Edson, telephone 301-402-7565) in order to update your assurance.

(6) Your November 24, 1999 report stated, "An education sub-committee was chosen with the task of developing a curriculum for training sessions for investigators, staff and IRB members. Also mandatory requirements demonstrating that investigators and IRB members have participated in appropriate training and understanding of regulations pertaining to human research will be instituted as part of the investigational policy at Michael Reese Hospital." OHRP is interested in the extent to which the training requirements described in your report have been implemented. Please respond. In your response please describe the educational program which was developed, how investigators and IRB members attending the training are being tracked, and how many individuals have completed the training.

(7) It appears that the 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.

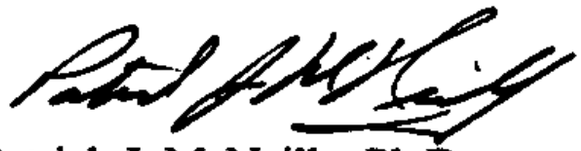
(8) Where HHS regulations require specific findings on the part of the IRB, such as (a) approving a procedure which alters or waives the requirements for informed consent [see 45 CFR 46.116(d)]; (b) approving a procedure which waives the requirement for obtaining a signed consent form [see 45 CFR 46.117(c)]; (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.

(9) OHRP recommends that institutions develop and distribute a handbook of IRB guidelines for research investigators. The handbook should include detailed information concerning (a) federal and institutional requirements for the protection of human research subjects; (b) the IRB's role and responsibilities; (c) the requirements and procedures for initial and continuing IRB review and approval of research; (d) the rationale and procedures for proposing that the research may meet the criteria for expedited review; (e) the requirements and procedures for verifying that research is exempt from IRB review; (f) the responsibilities of investigators during the review and conduct of research; (g) requirements and procedures for notifying the IRB of unanticipated problems or events involving risks to the subjects, as well as any other expected or unexpected adverse events;

(h) an explanation of the distinction between FDA requirements for emergency use of test articles versus HHS regulations for the conduct of human subjects research; (i) relevant examples and user-friendly forms for providing information to the IRB; and (j) a copy of the institution's MPA, the HHS humans subjects regulations (45 CFR Part 46), and *The Belmont Report*. Where appropriate, OHRP also recommends that IRBs develop written operating procedures to supplement its guidelines for investigators.

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

Sincerely,



Patrick J. McNeilly, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

Enclosure: NSABP audit report

cc: Dr. Anne Laumann, IRB Chair, Michael Reese Hospital
Ms. Joyce Washington, Michael Reese Hospital
Ms. Martha B. Maher, NSABP, NCI
Dr. Gregory Koski, OHRP
Dr. Melody Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Jeffrey Cohen, OHRP
Mr. George Gasparis, OHRP
Ms. Roslyn Edson, OHRP
Mr. Barry Bowman, OHRP