DEPARTMENT OF HEALTH & HUMAN SERVICES

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July 22, 2001

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RE: Human Subjects Protections Under Multiple Project Assurance (MPA) M-1011

Dear Dr. Miller, Dr. Dang, and Mr. Schaffer:

The Office for Human Research Protections (OHRP) has reviewed your July 21, 2001 letter describing your institution's corrective action plan to address the deficiencies cited by OHRP in its July 19, 2001 letter which was provided to you at OHRP's site visit exit interview last week. OHRP recognizes the extraordinary efforts that your faculty and staff have made to develop this corrective action plan and to begin the initial steps to improve your system for protecting human subjects.

OHRP acknowledges your report in the above-referenced letter that faculty and staff at signatory institutions under MPA M-1011 were directed to suspend all Federally supported human subject research on July 19, 2001, and were apprised that, in accordance with the required actions stipulated by OHRP's July 19, 2001 letter, (i) research activities in previously enrolled subjects could continue where it was in the best interests of individual subjects to do so; and (ii) enrollment of new subjects must cease immediately except in extraordinary cases approved in advance by OHRP.

OHRP Finding

Based on its review of your letter, OHRP finds that your institutions have developed a satisfactory corrective action plan to address all areas of noncompliance and concerns documented in OHRP's July 19, 2001 letter. OHRP notes the proposal to create a third institutional review board (IRB) at the East Baltimore Medical Campus, bringing the number of IRBs designated under MPA M-1011 to four, and the plan to provide IRB 101 training offered through Public Responsibility in Medicine and Research to all IRB members and staff.

OHRP Action

In view of the above finding, OHRP hereby reinstates the Multiple Project Assurance (MPA M-1011) for the Johns Hopkins University School of Medicine, the Johns Hopkins University School of Nursing, the Johns Hopkins Hospital, the Johns Hopkins Bayview Medical Center, the Gerontology Research Center of the National Institute of Aging-Bayview Campus, the Kennedy-Krieger Institute, and the Applied Physics Laboratory.

This reinstatement, effective immediately as of the date of this letter, provides the Assurance required by Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(a) for Federally supported research involving human subjects at the above MPA signatory institutions. The MPA will retain its previous expiration date of October 31, 2003.

Furthermore, in order to ensure adequate protections for human subjects at the covered institutions, in accordance with HHS regulations at 45 CFR 46.103, effective immediately as of the date of this letter, OHRP hereby restricts MPA M-1011 according to the following conditions and required actions:

(1) Effective immediately as of the date of this letter, the following categories of human subject research may resume:

(a) Any Federally supported research protocols (as well as any other research protocols covered by MPA M-1011) eligible for expedited review that were reviewed and approved appropriately by one of the IRBs designated under MPA M-1011.

(b) Any Federally supported research protocols (as well as any other research protocols covered by MPA M-1011) not eligible for expedited review that were reviewed (initial or continuing review) and approved by one of the IRBs designated under MPA M-1011 at a convened meeting, as required by HHS regulations at 45 CFR 46.108(b), during the past one-year period. To be

considered reviewed by the convened IRB, the minutes of the relevant IRB

meeting(s) must document a substantive individual review, approval action, and vote to approve for a given research protocol.

(2) All other Federally supported human subject research protocols (as well as any other research protocols covered by MPA M-1011) not eligible for expedited review are to remain suspended in accordance with OHRP's letter of July 19, 2001, until one of the IRBs designated under MPA M-1011 reviews and approves the research at a convened meeting, as required by HHS regulations at 45 CFR 46.108(b) and in accordance with the procedures described in the corrective action plan described in your July 21, 2001 letter. Certification of such IRB approval must be submitted in writing to the appropriate official(s) at the supporting Federal department or agency, in accordance with HHS regulations at 45 CFR 46.103(f).

For any project affected by this suspension, enrollment of new subjects must remain suspended except in extraordinary cases approved in advance by OHRP (OHRP continues to expect requests for such approvals to be rare). Furthermore, research activities involving previously enrolled subjects may continue only where it is in the best interests of the individual subjects enrolled in the research. Decisions regarding continuation of <u>currently enrolled subjects</u> are to be made by your institutions and do not require OHRP approval. Such decisions may be made for all subjects enrolled in a particular clinical trial, as a group, and should primarily be based upon maximizing patient welfare and safety.

(3) By August 10, 2001, the above institutions covered by MPA M-1011 must provide a complete list of all Federally supported research protocols that were suspended, including the project title, principal investigator name, IRB project number, and the Federal department or agency project number. The list should identify those projects for which it has been determined that research activities involving previously enrolled subjects may continue because it is in the best interest of the individual subjects. Please describe the procedures used to make such determinations.

(4) Until further notice, the above institutions covered by MPA M-1011 must submit to OHRP detailed monthly progress reports regarding implementation of their corrective action plan and education programs for all IRB members, all IRB staff, and all investigators. The first progress report, due August 31, 2001, should include the following:

(a) A status report on the implementation of each proposed corrective action. This summary should include copies of the various checklists proposed in your corrective action plan.

(b) A summary of the progress made in implementing the planned educational programs for all IRB members, all IRB staff, and all research investigators about the ethical principles and regulatory requirements for the protection of human subjects.

(c) A summary of the IRBs progress in reviewing all suspended research projects.

(d) Copies of the minutes of all meetings of the Johns Hopkins University School of Medicine (JHUSOM) IRBs since October 1, 2000 that were not available for review during OHRP's site visit, and of all IRB meetings convened since OHRP's site visit.

(e) Any revised written IRB policies and procedures.

(f) A complete list of all active IRB-approved protocols, including the project title, principal investigator name, IRB project number, and the Federal department or agency project number, if applicable, as of July 16, 2001 for the JHUSOM IRBs.

Additional OHRP Comments Regarding Your Corrective Action Plan

OHRP provides the following additional guidance and responses to issues raised in your July 21 letter:

(1) OHRP acknowledges your disagreement with findings (8) and (9) in OHRP's July 19, 2001 letter. However, your response provides no new information that would warrant modification of OHRP's finding. In particular, OHRP notes the following:

(a) Your report stated that "[t]he review process undertaken before a convened meeting is designed to assure a triage process which assures that all issues relevant to the review process are identified and documented prior to the convened meeting." OHRP's site visit findings do not support this statement.

(b) Your letter indicated that one site visit team member appeared to favor the executive subcommittee review process used by the IRBs designated under MPA M-1011. While the OHRP site visit team did not find the use of executive subcommittees to be objectionable in and of itself, the site visit team unanimously found that the executive subcommittee review process, which does not represent substantive and meaningful IRB review, was used to preempt review by the IRB at convened meetings for most research projects.

(c) Regarding your statements about the IRB review procedures described in your December 28, 2000 report to OHRP, please note that pending a response from

OHRP, such matters remain open. OHRP's Division of Compliance Oversight responds to all reports in writing.

(d) OHRP's review of your December 28, 2000 report, MPA M-1011, and your current IRB policies and procedures did not reveal that most research not eligible for expedited review was not reviewed by the IRB at convened meetings, as required by HHS regulations at 45 CFR 46.108(b). Only after a three-day site visit involving an extensive review of IRB records, interviews with IRB members and staff, and a review of audiotapes of recent IRB meetings did OHRP determine that initial review of most research by the convened IRB was inadequate.

(e) OHRP acknowledges that your December 28, 2000 report and your current IRB policies and procedures appear to indicate deficiencies in continuing review procedures. However, OHRP was unable to determine the extent and severity of the deficiencies in the IRBs' continuing review process until it conducted its site visit.

(2) OHRP acknowledges that HHS regulations at 45 CFR 46.115(a)(2) do not specify a time frame by which minutes of IRB meetings must be prepared. Nevertheless, OHRP finds that not preparing minutes for nearly all meetings of the JHUSOM IRBs for over 9 months is generally considered an unacceptable practice.

(3) OHRP acknowledges your request for specific examples of informed consent document deficiencies found during its site visit. OHRP will provide such information in writing within the next 4 weeks.

(4) OHRP acknowledges your plan to assess the composition of the IRB designated under MPA M-1011. OHRP encourages your institutions to engage in efforts to enhance the racial and ethnic diversity of your IRBs given the demographics of the populations served by your institutions. Such action would promote respect for the IRBs' advice and counsel in safeguarding the rights and welfare of human subjects within the communities served by your institutions.

Finally, OHRP yesterday offered, and your July 21 letter accepted, the immediate assistance of OHRP's Division of Education staff. Dr. Jeffrey Cohen, Director of the Division of Education, will arrange for on-site training by OHRP staff of IRB members, IRB staff, and investigators to begin as early as Monday, July 23, 2001.

OHRP appreciates the renewed commitment of your institutions to the protection of human subjects. Do not hesitate to contact me should you have any questions.

Sincerely,

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

cc: Mr. Ronald R. Peterson, President, The Johns Hopkins Hospital
Dr. Sue K. Donaldson, Dean, School of Nursing, JHU
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