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HAND-DELIVERED

July 19, 2001

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

Research Project: Mechanisms of Deep Inspiration-Induced Airway Relaxation
Project Number: AAC00-07-26-02
Principal Investigator: Dr. Alkis Togias
HHS Project Number: R01 HL61277 (Principal Investigator: Dr. Solbert Permutt)

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

As you know, the Office for Human Research Protections (OHRP) conducted an on-site evaluation of (i) the circumstances surrounding the death of a healthy volunteer subject who participated in the above referenced research project, and (ii) the human subject protection system at the Johns Hopkins School of Medicine (JHUSOM), the Johns Hopkins Bayview Medical Center (JHBMC), and the other signatory institutions covered by MPA M-1011 on July 16-18, 2001. The evaluation, conducted by 5 OHRP staff and with the assistance of 3 expert consultants and a representative from the U.S. Food and Drug Administration (FDA), included meetings with senior institutional officials, the three Chairpersons of the Institutional Review

Boards (IRBs), 21 IRB members, all IRB administrative staff, and several research investigators, including the principal investigator and co-investigators for the above-referenced research project. The evaluation involved review of IRB files for over 60 protocols, all available minutes of the IRB meetings since 1998, and the audiotapes of two recent JHUSOM IRB meetings.

In the course of the OHRP review, the IRB chairs, IRB members, and IRB administrative staff displayed a sincere commitment to the protection of human subjects. Furthermore, the volume of research reviewed and the amount of time and effort devoted to IRB activities by the IRB Chairs and staff indicate great dedication to the mission of the IRBs. Investigators demonstrated a culture of respect for the IRB process. The IRB Administrator and staff were very helpful and accommodating to OHRP during the site visit. In particular, OHRP greatly appreciates the efforts of the IRB Administrator and staff to extend the site visit schedule and make a large volume of IRB records available to OHRP on very short notice.

OHRP Findings Regarding Research Protocol Number AAC00-07-26-02, Mechanisms of Deep Inspiration-Induced Airway Relaxation

Based upon its review of your institutions' reports dated May 17, June 6, June 22, June 26, June 29, and July 13, 2001, as well as additional information obtained during the site visit from records reviewed and interviews with investigators and IRB members and staff, OHRP makes the following findings regarding the above-referenced research.

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.111(a)(1) and (2) require that in order to approve research an IRB shall determine that the risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and that risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may reasonably be expected to result. OHRP finds that the JHBMC IRB and the investigators conducting the research failed to ensure that risks to subjects were minimized and reasonable, as required by HHS regulations at 45 CFR 46.111(a)(1) and (2). In particular, OHRP notes the following:

(a) Prior to the research being approved by the IRB, the investigators and the JHBMC IRB failed to obtain published literature about the known association between hexamethonium and lung toxicity. Such data was readily available via routine MEDLINE and Internet database searches, as well as recent textbooks on pathology of the lung.

(b) Use of hexamethonium is not currently approved by the FDA for use in humans, and has never been approved by the FDA for administration via inhalation.

(c) Prior to approving the research, the JHBMC IRB failed to obtain sufficient information regarding the source, purity, quality, and method of preparation and delivery of the hexamethonium used in the research.

(d) The hexamethonium bromide used in the research was obtained by the investigators from Fluka US and was labeled "[f]or laboratory use only, not for drug, household, or other uses." The JHBMC IRB was not aware of this information before the investigators administered the hexamethonium to three subjects and the hospitalization of the third subject.

(e) Prior to its approval of the research, the JHBMC IRB did not receive or request from the investigators (i) any information regarding the pharmacology and toxicity of inhaled hexamethonium in animals; or (ii) sufficient information regarding the safety of inhaled hexamethonium in humans.

(2) HHS regulations at 45 CFR 46.108(b) require that, except when an expedited review procedure is used, the IRB must review proposed research at convened meetings at which a majority of the members are present, including at least one member whose primary concerns are in nonscientific areas. OHRP finds that the JHBMC IRB failed to review the research, which was not eligible for expedited review under HHS regulation at 45 CFR 46.110(b), at a convened meeting [see finding (8) below]. As a result, the JHBMC IRB failed to ensure that all criteria required for IRB approval under HHS regulations at 45 CFR 46.111 were satisfied.

(3) HHS regulations at 45 CFR 46.103(b)(4) and 46.108(a) require that the IRB review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. OHRP finds that the following changes to the research protocol were implemented by the investigators without IRB approval:

(a) The investigator initially changed the diluent for the hexamethonium solution from normal saline to distilled water starting with the first subject, and then further modified the solution by adding sodium bicarbonate in order to neutralize the pH starting with the second subject.

(b) The investigators failed to perform a Limulus test on each solution prior to administration to subjects as required by the IRB-approved protocol.

(c) The investigators changed the aerosol delivery system after the second subject's first administration.

(4) HHS regulations at 45 CFR 46.116 stipulate that no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. HHS regulations at 45 CFR 46.116(a) stipulate basic elements for such informed consent.

(a) OHRP finds that the informed consent document approved by the JHBMC IRB for the research failed to adequately describe the research procedures to be followed or identify procedures which were experimental, as required by HHS regulations at 45 CFR 46.116(a)(1). In specific, OHRP notes the following:

(i) The informed consent document failed to indicate that inhaled hexamethonium was experimental and not approved by the FDA. OHRP is particularly concerned that the hexamethonium was referred to as a "medication" in the informed consent document.

(ii) The informed consent document failed to describe the plan for escalating the inhaled methacholine dose during the screening phase of the research.

(b) OHRP finds that the informed consent document approved by the JHBMC IRB failed to adequately describe the reasonably foreseeable risks and discomforts associated with the research, as required by HHS regulations at 45 CFR 46.116(a)(2). OHRP finds that the investigators failed to provide a description of the possible pulmonary toxicity of hexamethonium to the subjects.

(5) HHS regulations at 45 CFR 46.116(b)(1) and (2) require that, when appropriate, the following additional elements of informed consent be provided to each subject:

(a) A statement that the particular treatment or procedure may involve risks to the subjects which are currently unforeseeable.

(b) A description of anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

OHRP finds that it would have been appropriate for the informed consent document for the research to include these elements.

(6) OHRP finds that the investigators failed to promptly report an unanticipated problem involving risks to subjects to appropriate institutional officials, the IRB, OHRP, and the head of the sponsoring agency as required by HHS regulations at 45 CFR 46.103(a) and (b)(5). In specific, the investigators failed to promptly report the cough, shortness of breath, and a decrease in pulmonary function experienced for 8 days by the first subject

exposed to hexamethonium. OHRP is particularly concerned that the investigators continued to expose additional subjects to inhaled hexamethonium before the symptoms in the first subject were resolved and before reporting the event to the JHBMC IRB.

(7) OHRP acknowledges and concurs with the following conclusions from your Report of Internal Investigation into the Death of a Volunteer Research Subject provided to OHRP on July 13:

(a) "[A]n adequate evidence base did not exist for the IRB to be confident that inhaled hexamethonium was safe for use in research subjects."

(b) "[T]he consent form [for the research] should not have been approved by the IRB."

(c) "[T]he death [of the third subject exposed to inhaled hexamethonium] was most likely the result of participation in the hexamethonium phase of the experiment."

OHRP Findings Regarding Human Subjects Protections Under MPA M-1011

Major Findings

(8) HHS regulations at 45 CFR 46.108(b) require that, except when an expedited review procedure is used, the IRB must review proposed research at convened meetings at which a majority of the members are present, including at least one member whose primary concerns are in nonscientific areas. OHRP finds that the JHUSOM and JHBMC IRBs (the IRBs) fail to review at convened meetings most research undergoing initial review that is not eligible for expedited review. As a result, the IRBs fail to ensure that all criteria required for IRB approval under HHS regulations at 45 CFR 46.111 are satisfied. Of note, the minutes and audiotapes of IRB meetings, and our discussions with IRB members and administrators, indicate that no review takes place at convened meetings for most protocols undergoing initial review. Most protocols are neither individually presented nor discussed at a convened meeting of any IRB.

(9) As OHRP noted in its letter of October 3, 2000 to your institutions, OHRP reiterates that 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. Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol that requires continuing review by the convened IRB.

OHRP finds that continuing review of research by the IRBs is not substantive nor meaningful. As with initial review of research, nearly all protocols undergoing continuing review are neither individually presented nor discussed at a convened meeting by the IRBs.

(10) HHS regulations at 45 CFR 46.115(a) require that an institution, or when appropriate, an IRB, shall prepare and maintain documentation of IRB activities, including minutes of IRB meetings. Furthermore, HHS regulations at 45 CFR 46.115(a)(2) require that such minutes be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution. OHRP finds that:

(a) For the JHUSOM IRBs, minutes of IRB meetings do not yet exist for 18 of the last 21 meetings dating back to October 2000.

(b) The minutes of meetings for all the IRBs often failed to document the basis for requiring changes in research. OHRP notes that IRB actions were not documented separately for each individual protocol. In addition, OHRP's review of protocols and IRB records revealed that some protocols had unresolved concerns following review by the IRB subcommittee, but there was no record in the minutes of IRB meetings of these concerns being addressed by full IRB.

(11) During its record review, OHRP found several protocol applications in which the IRB failed to receive or consider sufficient information for the IRBs to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111(a). For example, certain IRB applications provided only minimal information regarding (a) subject recruitment and enrollment procedures; (b) the equitable selection of subjects; (c) provisions to protect the privacy of subjects and maintain the confidentiality of data; and (d) the local context for research conducted in international settings.

(12) HHS regulations at 45 CFR 46.111(b) require the IRB to ensure that additional safeguards have been included in research to protect the rights and welfare of vulnerable subjects. OHRP finds that IRB records failed to demonstrate consistently the consideration of such safeguards.

Additional Findings

(13) HHS regulations at 45 CFR 46.107(e) stipulate that no IRB member may participate in the IRB's initial or continuing review of a project in which the member has a conflicting interest, except to provide information requested by the IRB. OHRP found instances in which IRB members inappropriately participated in the initial and continuing review of protocols for which they had a conflicting interest. As noted in OHRP's October 3, 2000 letter, OHRP strongly recommends that IRB members absent themselves from the meeting room when the IRB votes on research in which they have a conflicting interest, and such should be noted in the IRB meeting minutes.

(14) HHS regulations at 45 CFR 46.110(b)(2) permit use of expedited procedures for review of minor changes to previously approved research. OHRP finds that the IRBs routinely employed expedited procedures to review changes that exceed this limitation.

OHRP recommends that institutions adopt policies describing the types of minor changes in previously approved research which can be approved by expedited review in accordance with HHS regulations at 45 CFR 46.110(b)(2).

(15) HHS regulations at 45 CFR 46.116(a) delineate specific elements required for informed consent.

(a) OHRP found multiple instances where (i) required elements were omitted or inadequate; and (ii) there were discrepancies between the protocol application and the informed consent documents regarding the purpose, risks, and benefits of the research.

(b) OHRP is concerned that the IRBs encourage investigators to limit the length of informed consent documents, and as a result, important information is being excluded.

(16) HHS regulations at 45 CFR 46.116(b) require that, when appropriate, additional elements of informed consent be provided to each subject. OHRP found numerous instances where it would have been appropriate for the informed consent document to include one or more of these additional elements. In particular, the elements at 46.116(b)(2), (4) and (5) were the additional elements most frequently overlooked.

As previously stated in OHRP's letter of October 3, 2000, OHRP again strongly recommends that the informed consent document boilerplate used by the IRBs and checklist be modified to include the additional elements at 45 CFR 46.116(b).

(17) 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 documents approved by the IRBs often appeared to include complex language that would not be understandable to all subjects.

(18) OHRP is concerned that the boilerplate informed consent document is difficult to understand and contains information that may be irrelevant for certain research projects.

(19) OHRP is concerned that the current membership of the IRBs appears to lack the diversity, including consideration of race and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects, as required under HHS regulations at 45 CFR 46.107(a).

(20) With respect to the JHUSOM IRBs, OHRP is concerned that many of the above findings may be indicative of IRBs overburdened by the large volume of research for which it has oversight responsibility. It is OHRP's experience that such a large volume of human subjects research warrants more than two fully functional IRBs.

(21) HHS regulations at 45 CFR 46.103(b)(2) require that institutions provide sufficient staff to support the IRB's review and recordkeeping duties. OHRP is concerned that the level of staff support provided to the JHUSOM IRBs appears to be insufficient. It is OHRP's experience that the volume of human subjects research conducted by the institution warrants additional professional and clerical IRB staff members.

(22) HHS regulations at 45 CFR 46.404-407 require specific findings on the part of the IRB for approval of research involving children. OHRP's discussions with IRB members and its review of IRBs documents reveal no evidence that the IRB consistently makes the required findings when reviewing research involving children.

(23) HHS regulations at 45 CFR 46.305-306 require specific findings on the part of the IRB for approval of research involving prisoners. OHRP's discussions with IRB members and its review of IRB documents reveal no evidence that the IRB makes the required findings when reviewing such research.

(24) OHRP is concerned that the IRBs issue approval letters to investigators prior to receiving and confirming the adequacy of revisions required by the IRBs.

(25) HHS regulations at 45 CFR 46.116(d) require that the IRB find and document four specific criteria when approving waiver or alteration of some or all of the required elements of informed consent. OHRP's discussions with IRB members and its review of IRB documents reveal no evidence that the IRB consistently satisfies these requirements.

(26) OHRP is concerned that the Chairs and members of the IRBs appear to lack a detailed understanding of the specific requirements of the HHS regulations for the protection of human subjects. As a result, IRB determinations have sometimes deviated from these requirements.

(27) 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(b)(4) and (5):

(a) 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.

(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.

(28) OHRP is concerned about the adequacy of the IRB's present procedures for ensuring prompt reporting, review, and evaluation of unanticipated problems involving risks to subjects or others.

Additional OHRP Guidance

(29) As OHRP noted in its October 3, 2000 letter, OHRP again recommends that documentation for initial and continuing reviews conducted utilizing expedited review procedures include the specific permissible categories (see 63 FR 60364) justifying the expedited review.

(30) 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.

(31) As OHRP noted in its October 3, 2000 letter, 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).

OHRP Action

In view of the above determinations and in order to ensure adequate protections for human subjects at the covered institutions, in accordance with HHS regulations at 45 CFR 46.103,

OHRP hereby suspends 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.

The suspension of MPA M-1011 is effective immediately as of the date of this letter and removes the Assurance required by HHS regulations at 45 CFR 46.103(a) for all Federally supported research involving human subjects at the above MPA signatory institutions.

As result, all Federally supported research projects at the covered institutions must be suspended. 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 such approvals to be rare). Furthermore, research activities involving previously enrolled subjects may continue only where it is in the best interests of individual subjects. No suspended Federally supported research at these institutions may resume without OHRP reinstatement of the MPA, or approval by OHRP of an applicable Assurance.

Required Actions:

(1) JHUSOM, JHBMC, and all other institutions covered by MPA M-1011 must develop the following corrective action plans as a condition for OHRP consideration of reinstatement of the MPA:

(a) Satisfactory corrective action plans to address all deficiencies and concerns described above. In order to be considered satisfactory, such corrective action plans must include a plan for the convened IRB to review all research protocols not eligible for expedited review.

(b) A satisfactory plan to restructure the system for protecting human subjects under MPA M-1011. In OHRP's experience, such restructuring would necessarily include an enhanced institutional commitment to human subject protections, implementation of additional IRBs, and appointment of additional IRB Chairpersons.

(c) A satisfactory plan to ensure that all IRB members, all IRB staff, and all research investigators are appropriately educated, on an immediate and ongoing basis, about the regulatory requirements for the protection of human subjects.

(2) 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.

OHRP encourages JHUSOM and JHBMC to develop the corrective action plans expeditiously, and forward them to OHRP for review as soon as possible. OHRP is available to assist in the development and implementation of these corrective action plans. Do not hesitate to contact OHRP should you have any questions.

Sincerely,

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Compliance Oversight Coordinator
Division of Compliance Oversight

Michael Carome, M.D.
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