DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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May 26, 2004

Raphael Dolin, M.D.
Dean for Academic and Clinical Programs

Margaret Dale, J.D.
Associate Dean for Faculty Affairs

Harvard Medical School
Department of Research Issues
25 Shattuck St.
Gordon Hall, Room 206
Boston, MA 02115

RE: Human Research Subject Protections Under Multiple Project Assurance MPA-1240

Dear Dr. Dolin and Ms. Dale:

The Office for Human Research Protections (OHRP) has reviewed Harvard Medical School's (HMS) letter dated April 29, 2004. OHRP has determined that the corrective actions summarized below appropriately address the issues raised in OHRP's March 26, 2004 letter:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(f) require that an institution with an approved assurance shall certify that each *application* or proposal for research covered by the assurance has been reviewed and approved by the institutional review board (IRB). In reviewing IRB records, and in discussions with IRB members, IRB and administrators, OHRP found that the IRB frequently fails to review the grant application for proposed research.

Corrective Action: OHRP acknowledges that the HMS IRB staff will now ensure that primary reviewers receive the entire grant application, and will be expected to review it, and that the grant application will be available to all IRB members during the convened meeting of the IRB.

(2) OHRP found that the IRB occasionally approves research contingent upon

substantive modifications or clarifications without requiring additional review by the convened IRB. For example, in the 12/16/03 review of protocol #M11047-101, the IRB approved the protocol contingent upon information about the randomization process, services that suicidal subjects would receive, exclusion of pregnant women, and how stigmatization might affect family and community relationships. In addition, in the 10/24/00 review of protocol #M10757-106, the IRB approved the protocol contingent upon information about "consent by substituted judgement," what information would be used from the subjects, and a description of how consent was obtained.

Corrective Action: OHRP acknowledges that the HMS IRB has changed its procedures to ensure that IRB does not approve research contingent upon substantive modifications or clarifications without requiring additional review by the convened IRB. These procedures will require deferral of a protocol when the IRB requires submission of additional substantive or complex information or simple concurrence by the investigator is not a sufficient response to the stated contingencies.

(3) OHRP found that some informed consent documents reviewed and approved by the IRB failed to adequately address the following elements required by HHS regulations at 45 CFR 46.116 (a):

(a) Section 46.116(a)(1): a complete description of the procedures to be followed. In specific, the informed consent document for protocol #M11186-101 failed to describe that the researchers would correlate the student's video-based assessment with his or her performance on the OSCE and grades in the subsequent year. In addition, protocol #M10310-102 randomly assigned subjects to one of four treatment groups, and then subjects were given a survey; however, the informed consent document stated simply "if you wish to participate in this survey...." This informed consent document did not include an adequate description of the four treatment groups, and instead focused on the survey aspect of the research.

(b) Section 46.116(a)(2): A description of the reasonably foreseeable risks and discomforts. In specific, the informed consent document for protocol #M10635-101 stated that there were no risks or discomforts of the intervention; however, the manufacturer of the agent identified some potential risks (including allergy to product) which were not described in the informed consent document. In addition, the informed consent document for protocol #M10310-102 stated simply, "We anticipate no harm associated with this survey...." However, the informed consent document did not include an adequate description of the risks of the four treatment groups to which subjects would be randomly assigned.

Corrective Action: OHRP acknowledges that, if the research is ongoing, the informed consent documents for the above-referenced studies will be revised and reviewed by the HMS IRB. In addition, the HMS IRB has taken steps to help assure that informed consent documents include all of the elements required by HHS regulations at 45 CFR 46.116. These include posting an informed consent checklist and a sample informed consent document on the HMS IRB website and providing IRB members with the

informed consent checklist and a reviewer checklist to use in review of research and informed consent documents.

(4) HHS regulations at 45 CFR 46.116 require that informed consent information be in language understandable to the subject or the subject's legally authorized representative. OHRP found that many of the informed consent documents approved by the HMS IRB included complex language that would not be understandable to all subjects. For example: (a) the informed consent document for protocol #M10014-101 contained language such as "peripheral," "auto-immune disease," and "transient unconsciousness," (b) the informed consent document for protocol #M10635-101 included phrases such as "prophy," and "adhesion of microorganism;" and (c) the informed consent document for protocol #M10749-101 was supposed to be written at a 4th-grade level, but had words such as "participation," "organized," "securely," and "assessment."

Corrective Action: OHRP acknowledges that, if the research is ongoing, the informed consent documents for the above-referenced studies will be revised and reviewed by the IRB. In addition, pre-review of informed consent documents by IRB staff, as well as review as needed by a grade school teacher, will help ensure that the HMS IRB approves informed consent information that is in language understandable to the subjects.

(5) OHRP expressed concern that the current IRB membership appears to lack the diversity, including consideration of race, gender, 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 46.103(d) and 46.107(a).

Corrective Action: OHRP acknowledges that the HMS IRB has identified members and potential members to increase the diversity of the IRB.

(6) HHS regulations at 45 CFR 46.103(a) and (b)(5) require, among other things, that the IRB promptly report to OHRP any serious or continuing noncompliance with the regulations or the requirements or determinations of the IRB. At the March 25, 2003 review of the closure of protocols #M10018-101 and 020403-1 the HMS IRB discovered that the principal investigator had previously submitted an application for a different research project, did not hear back from the IRB, assumed the protocol was approved, and conducted the research without prior review and approval of the HMS IRB. This serious non-compliance was not reported to OHRP.

Corrective Action: OHRP acknowledges that HMS has now reported this incident to OHRP, and has instituted written procedures to ensure that any serious or continuing noncompliance is promptly reported to OHRP.

As a result, 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.

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

Sincerely,

Kristina C. Borror, Ph.D.
Director
Division of Compliance Oversight

cc: Dr. Joseph B. Martin, Dean of the Harvard University Faculty of Medicine
Dr. Carolyn M. Connelly, Director, Office for Research Subject Protection, HUMS
Dr. Julie E. Buring, Chair, Committee on Human Studies, HUMS
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Bernard Schwetz, OHRP
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Ms. Melinda Hill, OHRP
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