DEPARTMENT OF HEALTH & HUMAN SERVICES

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

Dear Dr. Dolin and Ms. Dale:

As you know, the Office for Human Research Protections (OHRP) conducted an on-site evaluation of human subject protection procedures at the Harvard Medical School (HMS) on March 17-19, 2004. The evaluation, conducted by 3 OHRP staff with the assistance of 1 consultant, included meetings with institutional officials, 7 Institutional Review Board (IRB) members, IRB administrative staff, and investigators supported by the Department of Health and Human Services (HHS). The evaluation involved review of IRB files for over 20 protocols, and the minutes of more than 6 IRB meetings at which more than 80 items were considered.

In the course of the OHRP review, the IRB chair, IRB members, and IRB administrative staff displayed an enthusiastic and sincere concern for the protection of human subjects and stated that they view themselves as providing a valuable service to subjects, the research community and the institution. Investigators demonstrated a culture of respect for the IRB process, and a genuine appreciation of the work that the IRB performs for the institution. The IRB administrative staff were helpful and accommodating to OHRP during the site visit, and demonstrated extensive knowledge of the

regulations.

Findings

(1) 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 IRB. In reviewing IRB records, and in discussions with IRB members, IRB and administrators, OHRP finds that the IRB frequently fails to review the grant application for proposed research.

(2) OHRP finds 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.

OHRP recommends the following guidelines in such cases: (a) When the convened IRB requests substantive clarifications or modifications regarding the protocol or informed consent documents that are directly relevant to the determinations required by the IRB under HHS regulations at 45 CFR 46.111, IRB approval of the proposed research should 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.

(3) OHRP finds 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 their performance on the OSCE and grades in the subsequent year. In addition, protocol #M10310-102 randomly assigned subjects to 1 of 4 treatment groups and then subject 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 4 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 4 treatment groups to which subjects would be randomly assigned.

(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 finds that many of the informed consent documents approved by 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;" (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."

(5) OHRP is concerned 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).

(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 it was 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 IRB. This serious non-compliance was not reported to OHRP.

Required Actions

HMS must develop a satisfactory corrective action plan to address the above determinations. OHRP is available to assist HMS in the development and implementation of these corrective action plans.

At this time, OHRP offers the following additional guidance.

(7) OHRP recommends that documentation for initial and continuing reviews conducted under an expedited review procedure include: (a) the specific permissible categories (see 63 FR 60364-60367 at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/expedited98.htm) justifying the expedited review; and (b) documentation of the review and action taken by the IRB chairperson or designated reviewer and any findings required under the HHS regulations.

(8)Written IRB policies and procedures should provide a step-by-step description with key operational details for each of the procedures required by HHS regulations at 45 CFR 46.103(b)(4) and (5). OHRP recommends that the HMS IRB written procedures be expanded to address the following:

(a) A specific procedure for how the IRB determines which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review, including specific criteria used to make these determinations (e.g., such criteria could include some or all of the following: (i) randomly selected projects; (ii) complex projects involving unusual levels or types of risk to subjects; (iii) projects conducted by investigators who previously have failed to comply with the requirements of the HHS regulations or the requirements or determinations of the IRB; and (iv) projects where concern about possible material changes occurring without IRB approval have been raised based upon information provided in continuing review reports or from other sources).

(b) A description of what steps are taken to ensure that investigators do not implement any protocol changes without prior IRB review and approval, except when necessary to eliminate apparent immediate hazards to subjects (e.g., this might be addressed through training programs and materials for investigators, specific directives included in approval letters to investigators, and random audits of research records).

(c) A description of which office(s) or institutional official(s) is responsible for promptly reporting to the IRB, appropriate institutional officials, any supporting Agency or Department heads, and OHRP any unanticipated problems involving risks to subjects or others. While OHRP acknowledges that the draft written procedures for the HMS IRB include a section on prompt reporting of unanticipated problems, the procedures only describe reporting of "adverse events," which does not encompass all unanticipated problems involving risks to subjects or others.

(9) HMS may wish to consider including additional pertinent information in its written IRB procedures, such as the following: (a) important definitions (e.g., the definition of *research*, *human subject*, and *minimal risk)*; (b) a description of procedures for implementing other relevant Federal regulations that apply to human subject research (e.g., FDA and HIPAA regulations); (c) procedures for selecting and appointing the IRB chairperson and members in

order to satisfy the requirements of HHS regulations at 45 CFR 46.107; (d) procedures for training and educating IRB members and staff and investigators; (e) a description of the required elements of informed consent and criteria for waiving or altering these requirements; and (f) procedures for ensuring that the IRB possesses sufficient knowledge of the local research context.

For additional guidance on IRB written procedures, see http://ohrp.osophs.dhhs.gov/humansubjects/guidance/irbgd702.htm

(10) OHRP recommends that each revision to a research protocol be incorporated into the written protocol. This practice ensures that there is only one complete protocol with the revision dates noted on each revised page and the first page of the protocol itself. This procedure is consistent with the procedure used for revised and approved informed consent documents which then supersede the previous one.

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
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