DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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November 27, 2000

Michael D. Rich
Executive Vice President
RAND
1700 Main Street
P.O. Box 2138
Santa Monica, CA 90407-2138

Tora K. Bikson, Ph.D.
Chair, Human Subjects Protection Committee
RAND
1700 Main Street
P.O. Box 2138
Santa Monica, CA 90407-2138

RE: Human Subjects Protections under Multiple Project Assurance (MPA) M-1031

Project Title: HIV Cost and Services Utilization Study
HHS Project #: U01-HS08578
Principal Investigator: Martin Shapiro, M.D.

Dear Mr. Rich and Dr. Bikson:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed your March 24, 1999 report regarding possible noncompliance with Federal regulations for protection of human subjects with respect to the above referenced research. OHRP apologizes for the delay in responding to your letter.

Based on its review of your report OHRP makes the following determinations:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(a) require that each institution engaged in human subjects research provide OHRP with a satisfactory Assurance to comply with the regulations, unless the research is exempt under 45 CFR 46.101(b).

OHRP finds that institutions whose sole involvement in the above referenced research was to refer eligible patients to the research team in accordance with the procedures stipulated by Enclosure 8 of your report (Referral Site Involvement in this Study) were not engaged in human subjects research and did not require an OPRR approved assurance.

(2) OHRP acknowledges that, in your March 24, 1999 report, RAND has agreed to ensure that any and all performance sites for its HHS supported human subjects research will hold applicable OHRP approved assurances prior to the initiation of research.

(3) HHS regulations at 45 CFR 46.305(a) require that the Institutional Review Board (IRB) make seven specific findings when reviewing and approving research involving prisoners as subjects. Furthermore, HHS regulations at 45 CFR 46.305(c) and 46.306(a)(1) require that institutions conducting such research certify to the Secretary of Health and Human Services that the IRB has made these seven findings.

(a) OHRP finds scant evidence that the RAND IRB made the findings required under 45 CFR 46.305(a) when it reviewed and approved the above referenced research.

(b) OHRP finds that RAND failed to certify to OPRR, acting on behalf of the Secretary of Health and Human Services, that the RAND IRB fulfilled its duties under 45 CFR 46.305(a) for the above referenced research, as required under 45 CFR 46.305(c).

(4) HHS regulations at 45 CFR 46.304(a) require that for the review of research involving prisoners as subjects at least one member of the IRB shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one IRB only one IRB need satisfy this requirement. The prisoner or prisoner representative must be present as a voting member, and should be present whenever the IRB reviews research involving prisoners as subjects (including initial review, continuing review, review of protocol amendments, and review of any unanticipated problems involving risks to the subjects or others).

(a) OHRP finds that the RAND IRB had discussions regarding the inclusion of prisoners in the research referenced above at its meeting on April 17, 1996. A prisoner representative was present for this discussion and approval of the involvement of randomly selected patients who are prisoners.

(b) OHRP finds that the prisoner representative participated in the discussion but did not vote on the actions of the RAND IRB.

(c) OHRP finds no evidence that any other review of the above referenced research included a prisoner or prisoner representative.

Action 1 - Required: By January 15, 2001, RAND must submit to OHRP satisfactory corrective plans to ensure that all future HHS supported research involving prisoners as subjects that is conducted by RAND complies with all requirements of HHS regulations at 45 CFR Part 46, Subpart C.

Action 2 - Recommended: Where HHS regulations require specific findings on the part of the IRB, such as (i) approving a procedure which alters or waives the requirements for informed consent [see 45 CFR 46.116(d)]; (ii) approving a procedure which waives the requirement for obtaining a signed consent form [see 45 CFR 46.117(c)]; (iii) approving research involving prisoners [see 45 CFR 46.305-306]; or (iv) approving research involving children [see 45 CFR 46.404-407], the HSPC should document such findings. OHRP strongly recommends that these findings be fully documented in the HSPC minutes, including protocol-specific information justifying each HSPC finding.

(5) OHRP finds that the institution does not have adequate written IRB policies and procedures that 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 (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.

(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 January 15, 2001, RAND must submit to OHRP revised written IRB policies and procedures that include operational details for each of the IRB activities referenced above. In order to assist RAND in this matter, please refer to the enclosed Guidance for Formulating Written IRB Policies and Procedures.

(5) 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 of the IRB are present, including one member whose primary concerns are in nonscientific areas. Furthermore, HHS regulations at 45 CFR 46.108(b) further stipulate that in order for research to be approved, the research must receive the approval of a majority of those present at the meeting.

Based upon documents provided with your report, OHRP is concerned that on occasion, the IRB conducts votes on IRB actions via e-mail. While IRB's may review and approve research via telephone conference call (see March 28, 2000 OPRR memorandum), the review and approval of research may not take place via e-mail.

Please provide a written response to this concern no later than January 15, 2001.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects.

Sincerely,

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

Enclosures: (1) Guidance for Formulating Written IRB Policies and Procedures
(2) March 28, 2000 OPRR memorandum regarding IRB meetings convened via telephone conference call

cc: Dr. James A. Thomson, RAND
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