DEPARTMENT OF HEALTH & HUMAN SERVICES

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November 27, 2000

Keith McLaughlin
Chief Executive Officer
Raritan Bay Medical Center
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Perth Amboy, NJ 08861

RE: Human Research Subject Protections Under Cooperative Project Assurance (CPA) T-4548
Research Projects: DAIDS Community Programs for Clinical Research on AIDS (CPCRA)

Dear Mr. McLaughlin:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed your August 13, 1999 report concerning research involving prisoners as subjects that was conducted by Raritan Bay Medical Center (RBMC). OHRP apologizes for the delay in responding to your report.

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

(1) OHRP acknowledges your report that (i) the RBMC Institutional Review Board (IRB) never intended to permit prisoners to be involved in the above referenced research that was supported by the Department of Health and Human Services (HHS); (ii) two subjects participating in CPCRA Study 039 subsequently became prisoners after being enrolled, and research data was collected from the subjects after they were incarcerated; and (iii) RBMC has notified all its investigators that research may not be conducted on prisoners. OHRP finds that this response adequately addresses the concerns regarding possible noncompliance with HHS regulations for the protection of human subjects at 45 CFR Part 46, Subpart C (*Additional DHHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects*).

In the event RBMC decides to revise its policy to permit involvement of prisoners in HHS-supported research, please note the following:

(a) HHS regulations at 45 CFR 46.305(a) require that the IRB make seven specific findings when reviewing and approving research involving prisoners as subjects. OHRP strongly recommends that these required findings be fully documented in the IRB minutes, including protocol-specific information justifying each IRB finding.

(b) HHS regulations at 45 CFR 46.305(c) and 46.306(a)(1) require that institutions conducting HHS-supported research involving prisoners as subjects certify to OHRP, acting on behalf of the Secretary of Health and Human Services, that the IRB has made the required findings under 45 CFR 46.305(a). Such certification should be submitted to OHRP for any CPCRA protocol for which the Division of Acquired Immunodeficiency Syndrome (DAIDS) has not specifically indicated that it is permissible to involve prisoners as subjects.

(c) HHS regulations at 45 CFR 46.306(b) require that for 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. When the convened IRB reviews research involving prisoners (including initial review, continuing review, review of protocol modifications, and review of unanticipated problems involving risks to subjects or others), the prisoner or prisoner representative must be present as a voting member. Where a particular research project is reviewed by more than one IRB, only one IRB needs to satisfy this membership requirement.

(2) HHS regulations at 45 CFR 46.108 require that, except when an expedited review procedure is used, the IRB review proposed research at convened meetings at which a majority of the members of the IRB are present. OHRP found that the IRB failed to meet this requirement for the following IRB meetings: November 15, 1996, April 18, 1997, April 17, 1998, and June 19, 1998. Thus, any actions taken at these meeting must be considered invalid. OHRP emphasizes that should the quorum fail during a meeting (e.g., those with conflicts being excused, early departures, loss of a nonscientist), the meeting is terminated from further votes unless the quorum can be restored.

(3) HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk and not less than once per year. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval. OHRP finds that the IRB failed to conduct continuing review at least annually for protocol numbers 57, 76, 78, 81, and 102.

If the IRB does not re-approve the research by the appropriately specified expiration date, subject accrual should be suspended pending re-approval of the research by the IRB. (Enrollment of new subjects cannot ordinarily occur after the expiration of IRB approval. Continuation of research interventions or interactions in already enrolled subjects should only continue when the IRB finds that it is in the best interests of individual subjects to do so. OHRP and IRBs must address on a case-by-case basis those rare instances where failure to enroll would seriously jeopardize the safety or well-being of an individual **prospective** subject.)

(4) OHRP finds that the RBMC IRB 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 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

(ii) 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, any Department or Agency head, and OHRP 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.

Required Action 1: By January 15, 2001, RBMC must submit to OHRP satisfactory corrective action plans that address findings (2)-(4) above. The corrective action plans should include revised IRB policies and procedures for the IRB that includes operational details of all procedures required by HHS regulations at 45 CFR 46.103(b)(4) and (5). To assist RBMC in revising its IRB policies and procedures please see the enclosed Guidance for Formulating Written IRB Policies and Procedures.

OHRP has the following additional concerns and questions regarding Project Number 039:

(5) HHS regulations at 45 CFR 46.116(a)(8) require that informed consent include a statement that ". . . refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled. . . ." The IRB-approved informed consent document states that "You may decide not to take part or to withdraw from the study at anytime without losing the benefits of your routine medical care." Since there could be penalties or loss of benefits that are not part of routine medical care, this language may not satisfy the requirements of HHS regulations at 45 CFR 46.116(a)(8). Please respond.

(6) The protocol listed as an inclusion criteria age greater than or equal to 13 years. Therefore this protocol might have included children. HHS regulations at 45 CFR 46.404-407 require specific findings on the part of the IRB for approval of research involving children. The documents provided for OHRP's review reveal no evidence that the IRB made the required findings when reviewing this research involving children. Please respond.

Where HHS regulations require specific findings on the part of the IRB, such as 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.

(7) OHRP notes that (a) the trial was fairly complicated and included, at the end, 5 overlapping cohorts; and (b) the informed consent document was used for all participants, regardless of the cohort they were to be enrolled in, making the document very difficult to understand. It may have increased understanding by having two separate consent documents, one for the first 400 enrollees (the "safety/virology" cohort) and one for the rest.

(8) The HHS regulations at 45 CFR 46.116 and 46.117 require that informed consent information be presented "in language understandable to the subject" and, in most situations, that informed consent be documented in writing. Where informed consent is documented in accordance with HHS regulations at 45 CFR 46.117(b)(1), the written informed consent document should embody, in language understandable to the subject, all the elements necessary for legally effective informed consent. Subjects who do not speak English should be presented with an informed consent document written in a language understandable to them.

(a) OHRP notes that the IRB rejected a Spanish language consent form saying "English version should be used and interpreted as per policy of RBMC."

(b) However, the RBMC Policy and Procedures Manual states that "It is strongly

recommended that the consent also be available in Spanish. If the subject does not understand English, then a consent should be written in the subject's language and a copy forwarded to the IRB." This is what the investigator did, but it was rejected for being in Spanish. Please explain.

(9) The 1996 version of the informed consent document noted that "there will be no personal identifiers on the tubes." Subsequent documents were changed to read "with usual protectors of identity." It is not clear what this means (usually blood drawn for medical reasons has identifiers) or why this change was made. Furthermore, this change was not pointed out in the table of revisions submitted with the protocol. Please explain.

(10) In early informed consent documents the drug was referred to as bisPOM PMEA; in later documents (most notably the addendum closing the protocol) it was referred to as adefovir. OHRP is concerned that this could have been confusing to subjects.

OHRP has the following additional concerns and questions regarding RBMC's overall system for protecting human subjects:

(11) The minutes of IRB meetings appear to indicate that little substantive review takes place at convened meetings. In particular, OHRP is concerned that the minutes of IRB meetings appear to reveal scant evidence that IRB approval of research is consistently based on consideration of the determinations required under HHS regulations at 45 CFR 46.111. For example, the IRB appears not to consider systematically and rigorously such issues as equitable selection of subjects and subject recruitment, and special protections required for vulnerable subjects. Please respond.

(12) Regarding IRB policies and procedures:

(a) The Policy and Procedure Manual for the IRB states that "Twenty-five percent of the membership shall constitute a quorum." As noted above, HHS regulations require that review of proposed research occur at meetings "at which a majority of the members of the IRB are present."

(b) The expedited review categories should be updated (see 63 FR 60364, copy enclosed).

(c) There is no mention of the criteria for IRB approval of research (see 45 CFR 46.111).

(d) The Elements of an Informed Consent provided to all investigators does not include all additional elements that should be added when appropriate, including additional costs to the subject, the consequences of withdrawal, and the numbers of subjects [see 45 CFR 46.116(b)].

These concerns should be addressed when RBMC revises its written IRB policies and procedures.

Please submit a written response to the concerns and questions cited in items (5) to (12) above no later than January 15, 2001.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me if you have any questions.

Sincerely,

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

cc: Dr. Sidney Kress, Chair, RBMC IRB
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