DEPARTMENT OF HEALTH & HUMAN SERVICES

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July 31, 2000

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Mr. Ira Clark
President
Public Health Trust
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Mr. Gus Godoy
Research Administrator
V.A. Medical Center
1201 N.W. 16th street
Miami, FL 33125

RE: Human Research Subject Protections Under the Multiple Project Assurance (MPA) M-1196
Research Projects Involving Prisoners

Dear Dr. Altman and Messrs. Clark and Godoy:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed your March 30, 2000 report concerning research involving prisoners as subjects that was conducted by the University of Miami (UM).

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

(1) Department of Health and Human Services (HHS) regulations at 45 CFR Part 46, Subpart C, stipulate additional requirements that must be satisfied by an institution and its Institutional Review Board (IRB) whenever it conducts research involving prisoners as subjects. OHRP finds that the University of Miami overall has made a good-faith effort to comply with these requirements over the past three years whenever it conducted research involving prisoners as subjects.

(2) HHS regulations at 45 CFR 46.304 require modification of IRB membership for review of research involving prisoners. In specific, 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.

(a) OHRP finds that a prisoner representative designated on the IRB membership rosters for UM's OHRP-approved Multiple Project Assurance participated in the IRBs' initial review of all research involving prisoners as subjects.

(b) OHRP acknowledges UM's self-reported finding that for some research projects involving a prisoners as subjects, a prisoner representative did not participate in the continuing review process. Furthermore, OHRP finds that UM IRB has taken appropriate corrective action by again performing continuing review of such research at a convened IRB meeting with a prisoner representative participating in the deliberations.

(c) OHRP notes that the IRB membership rosters submitted to, and accepted by, OHRP designate the prisoner representatives as a non-voting member on IRB-01, and as ex-officio members on IRB-02.

Action 1-Required: The procedures of the IRBs should be modified such that the prisoner representatives serve as full voting members whenever the IRBs review research involving prisoners as subjects. By August 28, 2000, please submit revised IRB membership rosters that designate the prisoner representatives as voting members.

(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. Based upon your report, and in particular, the minutes of recent IRB meetings where HHS-supported research involving prisoners as subjects, OHRP finds that the IRB is making and documenting the findings required under 45 CFR 46.305(a).

Action 2-Recommended: Where HHS regulations require specific findings on the part of the IRB, such as approving research involving prisoners, the IRB should document such findings. OHRP strongly recommends that these findings be fully documented in the IRB minutes, *including protocol-specific information justifying each IRB finding*. OHRP recommends that the UM minutes be expanded to included more protocol-specific information justifying the required findings for research involving prisoners as subjects.

(4) HHS regulations at 45 CFR 46.305(c) and 46.306(a)(1) require that institutions conducting 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 seven findings required by HHS regulations at 45 CFR 46.305(a). Furthermore, HHS regulations at 45 CFR 46.306(a)(2) require that the Secretary of Health and Human Services determine that the research involve solely activities described by HHS regulations at 45 CFR 46.306(a)(2)(A)-(D) (OHRP makes these determinations on behalf of the Secretary).

(a) OHRP acknowledges that under a prior agreement between OPRR and officials at the National Institute of Allergy and Infectious Disease (NIAID), responsibility for (i) receiving the institutional certifications required by HHS regulations at 45 CFR 46.305(c) and 46.306(a)(1), and (ii) making the determination required by HHS regulations at 45 CFR 46.306(a)(2) was delegated to NIAID officials for AIDS Clinical Trials Group (ACTG) protocols.

(b) OHRP finds that for some HHS-supported research (other than ACTG trials) approved for involvement of prisoners as subjects, UM (i) failed to provide certification to OHRP that the IRB fulfilled it duties stipulated under 45.305(a) as required by HHS regulations at 45 CFR 46.305(c) and 46.306(a)(1); and (ii) failed to obtain confirmation that OHRP judged the research to involve solely the permissible categories of research stipulated by HHS regulations at 45 CFR 46.306(a)(2)(A)-(D).

Action 3-Required: UM must suspend immediately involvement of prisoners in any HHS supported research projects that have not satisfied all requirements of HHS regulations at 45 CFR Part 46, Subpart C. For any project affected by this suspension action, enrollment of new prisoner subjects must cease immediately except in extraordinary cases approved in advance by OHRP (OHRP would expect approval requests for such cases to be rare). Furthermore, research activities involving previously enrolled subjects may continue only where it is in the best interests of individual subjects. This suspension must remain in effect for each affected protocol until the protocol has been reviewed, approved, and certified in accordance with all requirements of HHS regulations at 45 CFR Part 46, Subpart C.

Action 4-Required: By August 18, 2000, please provide OHRP with a list of all research protocols affected by this suspension. This list should identify those research projects where research activities involving previously enrolled prisoner subjects are allowed to continue because UM judged it to be in the best interests of individual subjects.

OHRP has the following additional questions and concerns concerning research involving prisoners as subjects conducted by UM:

(5) HHS regulations at 45 CFR 46.304 require that when reviewing research involving prisoners, 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. OHRP is concerned that the background and experience of the current prisoner representatives on the IRBs are insufficient for representing the perspective of prisoners. Furthermore, OHRP is concerned that the current duties of the prisoner representatives as employees of the Florida Department of Corrections may preclude them from serving in the capacity of prisoner representative on the IRB, because of actual or apparent conflicts of interests.

Action 5-Recommended: OHRP strongly recommends that UM carefully assess whether the current prisoner representatives on the IRBs are able to serve as truly unconflicted advocates for prisoners. If appropriate, UM should submit revised IRB membership rosters that identify new prisoner or prisoner representative members.

(6) OHRP notes that the UM guidelines for research involving prisoners as subjects permit the IRB to use an expedited review procedure. OHRP acknowledges that nothing in the HHS regulations for the protection of human subjects prohibits such a procedure for research involving prisoners as subjects. Nevertheless, OHRP recommends that the convened IRB review research involving prisoners as subjects.

OHRP has the following additional concerns regarding protocol number 99/464 (ACTG A5035, "Oncogenic Viral Pathogenesis and Cancer Risk Factors Among Patients with the Acquired Immunodeficiency Syndrome: A Prospective Cohort Study") :

(7) OHRP notes that this study appears to involve research on conditions particularly affecting prisoners as a class (see 45 CFR 46.306(a)(2)(C)). As such, the research would have required that OHRP, acting on behalf of the Secretary of Health and Human Services, consult with appropriate experts, including experts in penology, medicine, and ethics, and publish notice in the *Federal Register* of the intent to approve such research, before the research could involve prisoners. OHRP acknowledges that no subjects were enrolled in this research at UM. Nevertheless, OHRP is concerned that the IRB may have failed to appropriately categorize this research with respect to HHS regulations at 45 CFR 46.306(a)(2)(A)-(D) and to recognize the above requirements. Please respond.

(8) OHRP notes that a July 1998 UM memorandum concerning prisoner guidelines states that prisoners are not to be reimbursed for participation in research. However, the IRB-approved informed consent document for protocol number 99/464 states that subjects will receive $25 for each completed visit. Please explain this discrepancy.

OHRP has the following additional concerns regarding protocol number 99/598 (ACTG A5064, "A Pilot Study of Early Treatment Intensification of Antiretroviral Therapy (Version 1)"):

(9) OHRP notes that the IRB found this research to satisfy the criteria for permissible research involving prisoners as subjects stipulated by HHS regulations at 45 CFR 46.306(a)(2)(D)(i.e., research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject).

(a) OHRP is concerned that, given that (i) the inclusion criteria stipulated that all subjects had to have initiated therapy with a potent antiretroviral regimen occurring outside of a clinical trial; and (ii) this study was a pilot study assessing the effect of adding an additional antiretroviral drug, abacavir, there does not appear to be a sound basis for finding that this research has a reasonable probability of improving the health or well-being of the subjects.

(b) Furthermore, even if this research does have a reasonable probability of improving the health or well-being of the subjects, OHRP notes that half of the subjects are to be assigned to a placebo control group which may not benefit from the research. As such, the research would require that OHRP, acting on behalf of the Secretary of Health and Human Services, consult with appropriate experts, including experts in penology, medicine, and ethics, and publish notice in the *Federal Register* of the intent to approve such research, before the research could involve prisoners.

OHRP is concerned that the IRB may have failed to appropriately categorize this research with respect to HHS regulations at 45 CFR 46.306(a)(2)(A)-(D) and to recognize the above requirements. Please respond.

(10) HHS regulations at 45 CFR 46.305(a)(7) require that for research involving prisoners as subjects, where the IRB finds there may be a need for follow-up examination or care of subjects after the end of their participation, there must be adequate provision for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing subjects of this fact.

(a) Regarding IRB-01 protocol 99/464, OHRP notes that there are a number of potential complications from the research interventions, including severe hypersensitivity reactions, hypotension, kidney failure, liver failure, and even death, that could require long-term follow-up medical care.

(b) OHRP acknowledges that the IRB-approved informed consent document includes the following statement:

"If an injury results from your participation in this study, immediate and necessary medical care will be provided by the Department of Corrections. No other form of compensation is available from this institution, the sponsoring agency (National Institutes of Health), or the Department of Corrections."

While this statement appears to indicate that adequate provisions for follow-up examination and medical care will be available for acute injury to prisoner subjects, OHRP is concerned that this research protocol fails to include adequate provisions for follow-up medical care for potential long-term chronic medical conditions that may result from participation in the research, especially for those subjects who subsequently are released from prison.

For example, subjects suffering severe liver failure might need long-term follow up by a hepatologist, liver transplantation, and life-long immunosuppression therapy; subjects suffering hypotension could experience myocardial infarction and chronic congestive heart failure, and require long-term follow up by a cardiologist; and subjects suffering kidney failure might need long-term follow up by a nephrologist, chronic hemodialysis, kidney transplantation, and life-long immunosuppression therapy.

(c) Please provide a detailed response to OHRP's above concern. In your response, please describe (i) the provisions for providing follow-up care, including long-term subspecialty care, to prisoner subjects who suffer chronic complications from the research interventions that persist after their release from prison; and (ii) who will pay for this care (please note that requiring the subjects to pay for this follow-up care is not acceptable). Furthermore, OHRP strongly recommends that all other protocols involving prisoners as subjects be reassessed to confirm compliance with the requirements of HHS regulations at 45 CFR 46.305(a)(7).

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

(11) The minutes for the December 9, 1999 IRB-01 meeting indicate that for protocol # 99/607 ("Prospective, Randomized Study Comparing Vascular Embolization to External Fixation in Hemodynamically Unstable Patients with Pelvic Fracture") the IRB approved a waiver of informed consent in accordance with HHS regulations at 45 CFR 46.116(d).

(a) OHRP acknowledges that IRB minutes state that the IRB "agreed that this protocol met the waiver of informed consent requirements as specified under 45 CFR 46.116(d)." However, OHRP finds that this statement is not sufficient documentation of the four findings required under 45 CFR 46.116(d).

(b) Based on the title of the protocol, OHRP is concerned that this research does not satisfy all four criteria stipulated at 45 CFR 46.116(d). In particular, the title suggests that this research presents greater than minimal risk to the subjects. Please respond. In your response, please provide a complete copy of the IRB file for this research protocol including:

(i) The IRB-approved research protocol and grant application.
(ii) The IRB-approved informed consent documents.
(iii) The relevant IRB minutes, including initial review, continuing review, review of changes to the research or the informed consent document, and review of any adverse or unanticipated events.
(iv) The IRB's correspondence with the investigators.
(v) All continuing review reports.
(vi) A list of subjects (code number only) and date of enrollment.
(vii) A chronological summary of the dates of the IRB's actions.
(viii) A copy of any publications or presentations which were derived from this research project.
(ix) Any other pertinent information.

(12) OHRP is concerned that MU 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):

The procedures which the IRB will follow 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.

Please respond.

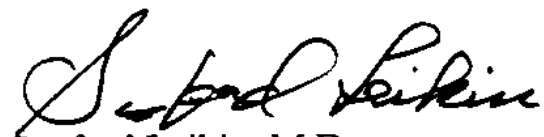
(13) HHS regulations at 45 CFR 46.404-407 require specific findings on the part of the IRB for approval of research involving children. Based upon its review of IRB minutes, OHRP is concerned that the IRB fails to consistently make the required findings when reviewing research involving children. OHRP strongly recommends that these findings be fully documented in the IRB minutes, including protocol-specific information justifying each IRB finding.

(14) Research protocols #99/392 and #99/393 were reviewed by the IRB at its meeting on August 16, 1999. Please inform OHRP as to their current status as to approval and continuing review. Also please provide OHRP with copies of the protocols and informed consent documents and, if available, assent documents.

Please submit to OHRP your written response to the above questions and concerns by September 11, 2000.

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

Sincerely,



Sanford Leikin, M.D.
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