DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY
OFFICE OF PUBLIC HEALTH AND SCIENCE

FOR US POSTAL SERVICE DELIVERY:
Office for Human Research Protections
6100 Executive Boulevard, Suite 3B01
National Institutes of Health (MSC 7507)
Rockville, Maryland 20892-7507

FOR HAND DELIVERY OR EXPRESS MAIL:
Office for Human Research Protections
6100 Executive Boulevard, Suite 3B01
Rockville, Maryland 20852

Telephone: 301-435-0062
FAX: 301-402-2071
E-mail: weilc@od.nih.gov

July 27, 2000

Dr. Alison F. Richard
Provost
Yale University
320 York Street
Room 117
New Haven, CT 06511

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1452

Research Project A: HIV Infection and Risk Behavior Among Incarcerated Women
Principle Investigator: Dr. Peter A. Selwyn
IRB Project Number: HIC #7101
HHS Award Number: U64-CCU109686

Research Project B: An Evaluation of Connecticut's Criminal Justice Diversion Program
Principle Investigator: Dr. Linda K. Frisman
IRB Project Number: HIC #10301
HHS Award Number: U1G SM52096

Dear Dr. Richard:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed your January 13, 2000 report concerning research involving prisoners as subjects that was conducted by Yale University.

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

(1) Department of Health and Human Services (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 in the IRB records provided that the Yale University IRB made the findings required by HHS regulations at 45 CFR 46.305(a) when it reviewed and approved the above referenced HHS-supported research projects that involved prisoners as subjects.

(b) OHRP finds that Yale University failed to certify to OPRR or OHRP, acting on behalf of the Secretary of Health and Human Services, (or to any other HHS office or official) that the IRB fulfilled it duties stipulated under 45.305(a) for HHS project number U64-CCU109686, as required by HHS regulations at 45 CFR 46.305(c) and 46.306(a)(1). OHRP acknowledges that this project has been completed.

(c) OHRP acknowledges that the Connecticut Department of Mental Health and Addiction Services provided to OPRR the certification required by HHS regulations at 45 CFR 46.305(c) and 46.306(a)(1) for HHS project number U1G SM52096 (HIC project number 10301). Furthermore, acting on behalf of the Secretary of Health and Human Services, OPRR determined that this project involved solely activities described by HHS regulations at 45 CFR 46.306(a)(2)(A).

(2) HHS regulations at 45 CFR 46.304(b) 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 a voting member of the IRB, 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 minutes of the October 27, 1993 IRB meeting indicate that the IRB initially approved HHS project number U64-CCU109686 without a prisoner or prisoner representative being present.

(b) OHRP acknowledges that the Connecticut Department of Mental Health and Addiction Services IRB included a prisoner representative when it conducted its initial review of HHS project number U1G SM52096 (HIC project number 10301).

Required Action 1: By August 31, Yale University must submit to OHRP satisfactory corrective action plans to ensure that all future HHS-supported research involving prisoners as subjects that is conducted by Yale University complies with all requirements of HHS regulations at 45 CFR Part 46, Subpart C.

Recommended Action 2: 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 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.

(3) HHS regulations at 45 CFR 46.103(f) require that an institution with an approved assurance shall certify that each *application* for research has been reviewed and approved by the IRB. In reviewing IRB records provided for HIC protocol number 7101, OHRP finds that a copy of the grant application for HHS project number U64-CCU109686 was lacking.

(4) 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 the review period.

OHRP finds that the IRB failed to conduct continuing review at least annually for HHS project numbers U64-CCU109686 and U1G SM52096. OHRP acknowledges that in no case did continuing review occur more than thirty days beyond the expiration date of the previous IRB review and approval.

Furthermore, for HHS project numbers U64-CCU109686 and U1G SM52096, which required review and approval by the convened IRB, the IRB incorrectly determined the time for the first continuing review based upon the date final approval was issued, rather than the date of the convened IRB meeting when the initial review was conducted, and conditional approval given.

If research is not timely re-approved by the IRB prior to the expiration of a review period, 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.)

(5) Continuing IRB review of research must be substantive and meaningful. In conducting continuing review of research not eligible for expedited review, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research, including (i) the number of subjects accrued; (ii) a description of any adverse events or unanticipated problems involving risks to subjects or others and of any withdrawal of subjects from the research or complaints about the research; (iii) a summary of any recent literature, findings obtained thus far, amendments or modifications to the research since the last review, reports on multi-center trials and any other relevant information, especially information about risks associated with the research; and (iv) a copy of the current informed consent document. Primary reviewer systems may be employed, so long as the full IRB receives the above information. Primary reviewers should also receive a copy of the complete protocol including any modifications previously approved by the IRB (see OPRR Reports 95-01 at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/hsdc95-01.htm). Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each

protocol undergoing continuing review by the convened IRB.

Based upon the minutes of IRB meetings provided for HIC protocol numbers 7101 and 10301, OHRP finds that continuing review of research by the IRB failed to satisfy all of these requirements for these protocols, as well as most other protocols. In particular, there is no documentation of discussions, separate actions, or separate votes for any protocols undergoing continuing review. Furthermore, it is unclear from the written IRB policies and procedures what documentation, if any, all IRB members receive prior to the meetings for protocols undergoing continuing review.

(6) OHRP finds that the Faculty of Arts and Science Committee (IRB M-1452-01) 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) 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, 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.

(7) OHRP finds that the Human Investigation Committees (IRB M-1452-02 and -04) do 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) and (5):

> (a) The procedures which the IRB will follow (i) for conducting its continuing review of research and for reporting its findings to the institution; and (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.
>
> (b) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, any Department or Agency head, and OHRP of (i) 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.

(8) OHRP finds that the Human Subjects Research Review Committee (IRB M-1452-03) 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) and (5):

(a) The procedures which the IRB will follow (i) for conducting continuing review of research and for reporting its findings and actions to the institution; and (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.

(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 3: By August 31, 2000, Yale University must submit to OHRP satisfactory corrective action plans that address findings (3)-(8) above. The corrective action plans should include revised IRB policies and procedures for each of the IRBs that include operational details of all procedures required by HHS regulations at 45 CFR 46.103(b)(4) and (5). To assist Yale University 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 HIC protocol number 7101:

(9) The continuing review form dated June 24, 1997, and completed by the investigator indicates that the protocol title was "Conduct of Studies Among High Risk Drug Injecting Women Incarcerated at a State Correctional Facility," whereas the original protocol title, which appears to have been maintained through the June 18, 1996, continuing review request form was "HIV Infection and Risk Behavior Among Incarcerated Women." There is no discussion in the IRB minutes or records reflecting the basis for this change, or seeking information about the change. Please explain.

(10) OHRP is concerned that the IRB-approved informed consent document for this research fails to include someone, in addition to the study investigators, for questions about research subjects' rights. OHRP considers it appropriate for informed consent documents to identify someone not associated with the research to be a contact for questions about research subjects' rights. Please respond.

OHRP has the following additional concerns and questions regarding HIC protocol number 10301:

(11) OHRP notes that (i) copies of the relevant grant application and survey instruments used in the research were first submitted to the IRB in December 1999; and (ii) the information

contained in these documents appears to be pertinent to IRB determinations required by HHS regulations at 45.CFR 46.111 and 46.305(a), and yet was not available to the IRB when it conducted its initial review in May 1998 and its first continuing review in June 1999. Please respond. In your response, please explain why these documents were not provided to the IRB prior to its initial review of this research.

(12) HHS regulations at 45 CFR 46.107(e) stipulate that no IRB member may participate in the IRB's initial or continuing review of a project in which the member has a conflicting interest, except to provide information requested by the IRB.

OHRP notes the following:

(a) The minutes of the May 27, 1998 IRB meeting list Dr. Howard Zonana as one of the members in attendance.

(b) The documents provided with your report include two articles apparently derived from this research that were co-authored by Dr. Zonana.

Please clarify whether Dr. Zonana participated as a prisoner representative on the IRB for the review of this protocol. The minutes of the May 27, 1998 IRB meeting also indicate that one person abstained from voting on this protocol. Please identify the person abstaining.

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

(13) Based upon review of minutes of IRB meeting provided with your report, OHRP is concerned that the IRB approval of research may not be consistently based on consideration of the determinations required under HHS regulations at 45 CFR 46.111. In specific, it appears that the IRB may not consider systematically and rigorously such issues as equitable selection of subjects and subject recruitment, privacy and confidentiality protections, and special protections required for vulnerable subjects. Please respond.

(14) In reviewing the IRB files for HIC protocol numbers 7107 and 10301, OHRP is concerned that the IRB approved research contingent upon substantive modifications or clarifications without requiring additional review by the convened IRB. OHRP recommends the following guidelines in such cases: (i) When the convened IRB requests substantive clarifications, protocol modifications, or informed consent document revisions, IRB approval of the proposed research must be **deferred**, pending subsequent review by the convened IRB of responsive material. (ii) 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. Please respond.

(15) HHS regulations at 45 CFR 46.115(a)(2) require that minutes of IRB meetings include a written summary of the discussion of controverted issues and their resolution. OHRP is concerned that the minutes of IRB meetings appear to rarely include such discussions. Please

respond.

(16) HHS regulations at 45 CFR 46.404-407 require specific findings on the part of the IRB for approval of research involving children. OHRP is concerned that the minutes of IRB meetings appear to reveal little evidence that the IRB makes the required findings when reviewing research involving children. Please respond.

(17) With respect to the written policies and procedures for the Faculty of Arts and Science Committee (IRB M-1452-01) :

(a) On page 4, first paragraph, lines 1-2, OHRP notes the following statement: "[I]t is unnecessary to submit an entire grant application...." This statement appears inconsistent with the requirements of HHS regulations at 45 CFR 46.103(f) that an institution with an approved assurance shall certify that each *application* for research has been reviewed and approved by the IRB. Please respond.

(b) On page 5, first paragraph, OHRP notes that the Psychology Subject Pool is described as containing "individuals below the age of consent in Connecticut...." Please describe the procedure that is followed for obtaining parental permission for such subjects.

(c) On page 6, second complete paragraph, OHRP notes a discussion of informed consent for research involving deception. Please note that because such research requires alteration of some of the required elements of informed consent, the IRB must make and document the findings required by HHS regulations at 45 CFR 46. 116(d). Please acknowledge the IRBs understanding of these requirements.

(d) On Page 10, paragraph entitled "**Changes in Existing Protocols**", OHRP notes the following statement: "The Committee must be notified of significant changes occurring to an existing *protocol*." OHRP is concerned that this policy is not in accordance with HHS regulations at 45 CFR 46.103(b)(4)(iii) which require that all changes (not just "significant changes") be reviewed and approved by the IRB prior to their initiation, except when necessary to eliminate immediate hazards to the subjects. Please respond.

(18) With respect to the written policies and procedures for the Human Investigation Committees (IRB M-1452-02 and -04)(i.e., Human Investigation Committee Guidelines):

(a) On page C.1, first paragraph, OHRP notes the description of the requirements for preparation of protocols. It appears that submission to the IRB of a complete copy of any Federal grant application is not a requirement. Please respond.

As previously noted above, HHS regulations at 45 CFR 46.103(f) require that an institution with an approved assurance shall certify that each *application* for research has been reviewed and approved by the IRB.

(b) HHS regulations at 45 CFR 46.108(b) require that initial review and approval of research be conducted by a convened quorum of the IRB, unless an expedited review procedure is permissible. HHS regulations do not permit research activities to be started, even in an emergency, without prior IRB review and approval [see 45 CFR 46.103(b), 46.109, and 46.116(f) and OPRR Reports 91-01 (http://ohrp.osophs.dhhs.gov/humansubjects/guidance/hsdc91-01.htm)]. When emergency medical care is initiated without prior IRB review and approval, the patient may not be considered a research subject. Such emergency care may not be claimed as research, nor may any data regarding such care be included in any report of a research activity. When emergency care involves investigational drugs, devices, or biologics, U.S. Food and Drug Administration (FDA) requirements must be satisfied.

OHRP is concerned that the description of the procedure for "interim approval" of research on page G.3 fails to comply with these HHS regulatory requirements. In specific, OHRP notes that the policy permits (i) the IRB Chair, in consultation with one or two other IRB members, to approve commencement of a research protocol before it has been reviewed and approved by a convened quorum of the IRB; and (ii) in rare cases, investigators who determine that the well-being of the patient would be seriously compromised by delay to assume interim IRB approval exists and proceed with the research.

Please respond.

(c) On page H.2, last paragraph, OHRP notes the following statement: "There are some circumstances under which adolescents may consent without parental involvement to participation in minimal risk studies (e.g., questionnaires, withdrawal of very small amount of blood)."

OHRP emphasizes that parental permission for research may be waived for children (the HHS regulations do not distinguish subsets of children such as adolescents) only if the IRB makes and documents the findings required by HHS regulations at 45 CFR 46.116(c), 46.116(d), or 408(c). Please acknowledge the IRBs' understanding of these requirements.

(d) On page I.2, first paragraph, OHRP notes the following statement: "An investigator may dispense with informed consent if the human subject is confronted with a life-threatening medical crisis requiring use of the investigational drug or device, the subject is unable to communicate consent, and there is no time to obtain consent from the subject's legal representative."

This policy does not appear to comply with the requirements of HHS regulations at 45 CFR 46.116. Please respond.

Please note that nothing in the HHS regulations at 45 CFR Part 46 is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable Federal, State, or local law.

Please do not hesitate to contact me if you have any questions.

Sincerely,

Carol J. Weil, J.D.
Compliance Oversight Coordinator
Division of Human Subject Protections

Enclosure: IRB Guidance document

cc: Dr. Melody Lin, OHRP
Dr. Michael Carome, OHRP
Dr. J. Thomas Puglisi, OHRP
Ms. Michele Russell-Einhorn, OHRP
Ms. Freda Yoder, OHRP
Dr. Clifford Scharke, OHRP
Mr. Peter Iovene, APT Foundation
Mr. Richard Rottman, Community Consultation Board
Dr. Selby Jacobs, Connecticut Mental Health Center
Dr. Vincent Gracco, Haskins Laboratories
Dr. Ethan Nadel, John B. Pierce Laboratory, Inc.
Ms. Sarah Cohn, Yale
Ms. Suzanne K. Polmar, Yale
Dr. Linda Frisman, Yale
Dr. Peter Selwyn, Yale
Dr. Marianne Lafrance Yale
Dr. Maurice Mahoney, Yale
Dr. Douglas Olsen, Yale
Dr. Robert Lange, Yale
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James McCormack, FDA