DEPARTMENT OF HEALTH & HUMAN SERVICES

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November 8, 2000

Dr. Alison F. Richard
Provost
Yale University
47 College Street
New Haven, CT 06520

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 #7107
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) has reviewed your August 30, 2000 report concerning the above-referenced research projects and recent changes in Yale University's (Yale's) system for the protection of human research subjects.

OHRP finds that Yale has implemented the following Required or Recommended Actions Stipulated in OHRP's letter of July 27, 2000:

(1) The Institutional Review Board (IRB) Operations Manual (Manual) at Section IV(C)(2) appropriately describes the findings required for prisoner research under Department of Health and Human Services (HHS) regulations at 45 CFR 46.305(a), and the importance of documenting these findings. Furthermore, OHRP acknowledges Yale's commitment that

each IRB will ensure that a voting prisoner representative is present whenever the IRB reviews research involving prisoner subjects.

(2) OHRP acknowledges the efforts of Yale to train IRB staff and investigators about the need to document in IRB minutes protocol-specific findings required by the HHS regulations, such as the requirements for waiving informed consent or documentation of consent, and the requirements for approving research involving prisoners or children.

(3) OHRP acknowledges that all four Yale IRBs now receive and review copies of Federal grant applications in accordance with the requirements of HHS regulations at 45 CFR 46.103(f), as set forth in the Manual and investigators' guides.

(4) OHRP acknowledges that the Yale IRBs have revised their continuing review procedures to ensure that: (a) appropriate review period determinations are made for each protocol; (b) continuing review will occur within one year from the date of the last convened IRB review, not from the date revisions required by the IRB for approval were accepted; and (c) continuing review will be substantive and meaningful.

(5) OHRP finds that Yale has revised its IRB policies and procedures for all four IRBs so that they adequately describe the operational details of all procedures required by HHS regulations at 45 CFR 46.103(b)(4) and (5).

OHRP finds that Yale has implemented the following corrective actions which address the additional concerns raised in OHRP's letter of July 27, 2000:

(6) OHRP acknowledges Yale's statement, in response to OHRP's expressed concern, that all Yale IRBs now require identification in informed consent documents of a contact other than the investigator for questions about research subjects' rights.

(7) OHRP acknowledges that the Yale Manual requires review of revisions to a protocol at convened IRB meetings, except for specific revisions (i.e., editing provided in writing) stipulated by the IRB, which may be reviewed by the Chair or Chair's designee on the IRB.

(8) OHRP acknowledges Yale's statement that the recent minutes of meetings of all four Yale IRBs include documentation of the discussion of controverted issues and their resolution, as required by 45 CFR 46.115(a)(2). OHRP requests that Yale submit to OHRP the minutes of the last three meetings of each of the four IRBs.

(9) OHRP acknowledges that Yale has developed a Protocol Review Criteria Checklist for use by IRB primary reviewers and by all members during IRB meetings, to ensure systematic review by the IRBs of the criteria for approval of research under HHS regulations at 45 CFR 46.111.

(10) OHRP acknowledges that Yale has (a) developed IRB Worksheets for Studies Involving Children; (b) revised Manual provisions regarding the required findings for research involving children; and (c) taken steps to educate IRB members about special protections for vulnerable populations of subjects, including children.

(11) OHRP acknowledges Yale's efforts, in developing the Waiver of Informed Consent Checklist in the Manual, to ensure that appropriate findings are made and documented when the IRB considers approval of research involving deception, in accordance with the requirements of HHS regulations at 45 CFR 46.116(d).

(12) OHRP acknowledges that the Faculty of Arts and Sciences (FAS) Human Subject Committee's Investigator's Guide has been changed to reflect the requirement for IRB review and approval of all (not just significant) changes, and that IRB guidance in the Manual attempts to educate investigators about this requirement.

(13) OHRP acknowledges that Yale has modified its IRB policies and procedures by deleting the description of an "interim approval" procedure, formerly at page G.3 of the Human Investigation Committee (HIC) Guidelines, and the discussion of waiver of informed consent to provide an investigational drug or device in a life-threatening crisis, formerly at page I.2 of the HIC Guidelines.

(14) OHRP acknowledges that Yale has modified its IRB policies and procedures to ensure that waiver of informed consent for adolescents does not occur in the absence of the required findings for research involving children.

(15) OHRP acknowledges that Yale has updated its investigator guidelines with the current list of research categories eligible for expedited review (see 63 FR 60364).

OHRP makes the following specific findings with respect to the HIC IRB's Project Number 7107 and 10301:

(16) OHRP acknowledges Yale's finding that the IRB vote to approve a change in title for project #7107 following the addition of a Hepatitis-C arm to the study was not documented in the IRB minutes.

(17) Yale's investigation appears to be inconclusive as to whether copies of original, non-published survey instruments were made available to the IRB when it conducted initial review of HIC Project Number 10301. OHRP acknowledges the HIC's intention to ensure that copies of nonstandard instruments are provided to IRB members prior to the meeting, and that copies of all materials provided to reviewers are retained in the protocol file.

(18) OHRP acknowledges Yale's finding that Dr. Zonana had no involvement in the research related to Project Number 10301, and that the two articles provided to OHRP that

were co-authored by Dr. Zonana were not in any way derived from research conducted under Project Number 10301.

OHRP has the following remaining concerns, questions and recommendations about Yale's system for human subject protections:

(1) Yale's letter of August 30, 2000 acknowledges that the HIC does not supply standard, published survey instruments to IRB members when such instruments are part of a protocol submitted for initial review. This practice may prevent some IRB members, particularly non-scientists who are not acquainted professionally with the instruments, from making the determinations required for IRB approval of research under HHS regulations at 45 CFR 46.111.

Required Action 1: Yale must submit to OHRP a corrective action plan to ensure that all IRB members will have access to relevant survey instruments in order to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111.

(2) Regarding the Psychology Subject Pool described in the FAS policies and procedures (page 5), your letter of August 30, 2000 (page 12) indicates that all Psychology Pool subjects are eligible for waiver of parental permission under 45 CFR 46.116(d), but the IRB has not appropriately documented such waivers. OHRP acknowledges that the new FAS "Studies Involving Children Worksheet" facilitates discussion of the basis for a waiver of parental permission by the IRB. However, it is not clear that literally every psychology pool protocol satisfies the requirements of HHS regulations at 45 CFR 46.116(d)(3) (i.e., "the research could not practicably be carried out without the waiver or alteration" of the consent requirements). Please respond.

(3) HHS regulations at 45 CFR 46.305(c) and 46.306(a)(1) require that institutions conducting prisoner research certify to the Secretary of Health and Human Services that the IRB has made findings required by HHS regulations at 45 CFR 46.305(a). This certification requirement is identified as an IRB obligation in Yale's IRB Compliance Plan, Section V(C). OHRP recommends that this certification requirement be included in the Manual as well.

(4) 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 research interests and academic affiliations of the current prisoner representative on IRB 0-2 and IRB-04, Dr. Howard Zonana, may create actual or apparent conflicts of interest which could affect his role as prisoner representative. Please respond. In formulating your response, OHRP recommends that Yale consider appointing one or more prisoner representatives to its IRBs who are clearly free of such apparent conflicts.

Please provide the information requested no later than December 7, 2000.

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,

Carol J. Weil, J.D.
Division of Compliance Oversight

cc: Dr. Greg Koski, OHRP
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