DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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November 27, 2000

Peder J. Estrup
Dean of Graduate School and Research
Brown University
Graduate School
Box 1867
Providence, PI 02912

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1411

Research Project: Learning Disabilities: Symptom Permanence and Consequences
Principal Investigator: Lewis Lipsitt
HHS Project Number: 5 R01 NS35208-04

Research Project: High-Risk Behaviors and the Prevalence of STD's among Women Prisoners at the Women's State Penitentiary in Metro Manila
Principal Investigator: Kenneth Mayer
HHS Project Number: 3 D43 TW00237-05

Dear Dr. Estrup:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed your February 11, 2000 report concerning research involving prisoners as subjects that was conducted by Brown 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 Brown 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 Brown 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 5 R01 NS35208-04, and for HHS project number 3 D43 TW00237-05 as required by HHS regulations at 45 CFR 46.305(c) and 46.306(a)(1). OHRP acknowledges that this second project has been completed.

(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).

OHRP finds that the minutes of the March 18, 1996 and March 17, 1997 IRB meetings indicate that the IRB approved HHS project number 3 D43 TW00237-05 without a prisoner or prisoner representative being present.

(3) OHRP acknowledges that Brown University determined that 8 additional protocols involved prisoner subjects but were not in compliance with the requirements of HHS regulations at 45 CFR Part 46, Subpart C. The IRB informed the investigators that the protocols did not consider additional protections required by Subpart C and "requested modification....to the active protocols..."

Required Action 1: By January 15, 2001, Brown 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 Brown 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 approving research involving prisoners (see 45 CFR 46.305-306), 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.

(4) 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 these protocols, OHRP finds that a copy of the grant application was lacking.

(5) 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 HHS protocol number 5 R01 NS35208-04.

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.)

(6) OHRP finds that the Brown University IRB does not have adequate written IRB policies and procedures for 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.
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> (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 January 15, 2001, Brown University must submit to OHRP satisfactory corrective action plans that address findings (4)-(6) 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 Brown 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 HHS Project Number 5 R01 NS35208-04:

(7) HHS regulations at 45 CFR 46.116 (a)(1) require that the informed consent document include, among other things, an explanation of the purposes of the research. OHRP is concerned that the IRB-approved informed consent document lacks an adequate explanation of the purposes of the research. In specific, although the focus of this study is on learning disabilities, there is nothing about learning disabilities in the informed consent document. Please respond.

(8) It appears that several documents referenced in the protocol were not provided to the IRB, including most of the study questionnaires, the contact protocol, a letter encouraging prospective subjects to participate, and a letter signed by the principal investigator to be read to the subject at the time of obtaining consent. OHRP notes that 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. Please respond. In your response, please explain why these documents were not provided to the IRB prior to its initial review of this research.

OHRP has the following additional concerns and questions regarding HHS Project Number 3 D43 TW00237-05:

(9) The IRB-approved protocol states that subjects will be approached for enrollment by "their primary physician" and that the questionnaire will be administered by this person. However a letter to the IRB about the Philippines notes the "...dismal state of prison health facilities...." It appears from other documents that the physician will be someone from the Philippine General Hospital; how this person could have been considered to be the inmate's "personal physician" is not clear. Furthermore, a letter from Sharon D'Antuono to Dorinda Williams has a note at the bottom (by Ms. Williams?) stating that "Sharon confirmed that all elements of the project would be performed by the Brown research team." Please clarify whether physicians at the Philippine General Hospital were part of the Brown research team.

(10) 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. It was not clear from the protocol and other documents in which language(s) the study or informed consent process would be conducted. The interview is partially translated into Tagalog, but there is no mention in the protocol about language, and the informed consent document is in English. Please respond.

(11) The IRB noted in the minutes of its February 26, 1996 meeting that the hospital involved in data collection (Philippine General Hospital) might need a Single Project Assurance. This apparently was never obtained. HHS regulations at 45 CFR 46.103(a) require that each institution engaged in human subjects research that is conducted or supported by the Department of Health and Human Services (HHS) provide an Assurance to OHRP. An institution is usually considered engaged in research when its staff, facilities, or private records of identifiable individuals are utilized in the conduct of the research. Furthermore, under its MPA (see Part 2, Section II.K) Brown University was responsible for ensuring that all affiliated institutions obtained approval for such Assurances when appropriate. Please respond.

(12) On February 21, 1996 the IRB asked that the consent form be changed to "...include a reference to the fact that there will be questions dealing with activities in which the subjects engaged prior to incarceration." This change does not appear to have been made. Please respond.

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

(13) 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 that IRB member Ms. Alice Tangredi-Hannon is the Director of the Office of Research Administration (ORA). OHRP is concerned that having the ORA Director serve as a voting member of the IRB may result in real or apparent conflicts of interest. Please respond.

(14) With respect to the written policies and procedures for Brown Faculty, Staff, and Students listed in the "Important Information Regarding Human Subject Research":

(a) OHRP notes that the IRB does not require the principal investigator to submit the grant application, just a summary, and the IRB asks the principal investigator to "limit protocols to two pages whenever possible." This 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. Furthermore, OHRP is concerned that limiting protocols to two pages may prevent the IRB from receiving sufficient information to make all determinations required by HHS regulations at 45 CFR 46.111, as well as by Subpart B, C, and D. Please respond.

(b) It appears from documents that the principal investigator determines what type of review takes place (exempt, expedited, full board.) This determination should be made by the IRB (or some authority other than the investigator). Please explain.

Please submit a written response to the concerns and questions cited in items (7) to (14) above no later than January 15, 2001. If upon further review of the concerns and questions, Brown University identifies additional instances of non-compliance with the HHS regulations for protection of human subjects, please include detailed corrective action plans to address the noncompliance.

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

Enclosure

cc: Dr. Dan Brock, Chairperson, IRB, BU
Ms. Dorinda E. Williams, IRB Administrator, BU
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael A. Carome, OHRP
Dr. J. Thomas Puglisi, OHRP
Dr. Jeffrey M. Cohen, OHRP
Dr. Katherine Duncan, OHRP
Ms. Freda Yoder, OHRP
Dr. Clifford C. Scharke, OHRP
Mr. Barry Bowman, OHRP