



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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November 29, 2011

Clyde L. Briant, Ph.D.
Vice President for Research
Office of the Vice President for Research
Box 1937
Brown University
Providence, RI 02912

RE: Human Research Subject Protections under Federalwide Assurance FWA-4460

Dear Dr. Briant:

The Office for Human Research Protections (OHRP) conducted an on-site evaluation of human subject protection program at Brown University (Brown), from August 15, 2011 – August 17, 2011. The evaluation was conducted as part of our program to evaluate human subjects protection programs of institutions that receive Department of Health and Human Services (HHS) support for research in compliance with 45 CFR part 46. The evaluation, conducted by four OHRP staff with the assistance of one consultant, included meetings and interviews with senior institutional officials, institutional review board (IRB) Chairs, IRB members, the administrative staff of the IRB and principal investigators that conduct HHS-supported research. During the evaluation, we reviewed IRB files for over 40 HHS-supported research studies, IRB meeting minutes, and IRB written policies and procedures.

First, we note that the IRB chairpersons, IRB members and staff displayed an enthusiastic and sincere commitment to the protection of human subjects at Brown. We appreciate how helpful and accommodating the Brown IRB staff was during our visit.

Based on review of your research records, interviews and follow-up clarifications (dated August 29, 2011), we make the following determinations:

A. Determinations regarding your institution's system for protecting human subjects

- 1) We reviewed the written IRB procedures and note that they were primarily instructions for writing and submitting research protocols, and lacked any substantive information regarding the IRB's policies and procedures as required by HHS regulations at 45 CFR 46.103(b)(4) and (5). Written IRB procedures must include key operational detail for each of the items listed in HHS regulations at 45 CFR 46.103(b)(4) and (5). We determine that the IRB lacks substantive written policies and procedures as required by HHS regulations at 45 CFR 46.103(b)(4) and (5).

Required Action: Please provide written IRB procedures that include key operational detail for each of the items listed in HHS regulations at 45 CFR 46.103(b)(4) and (5). For assistance with preparing appropriate IRB written procedures, please refer to the "Guidance on Written IRB Procedures" at <http://www.hhs.gov/ohrp/policy/irbgd107.html>.

- 2) We note that for several studies, informed consent was waived without documenting the appropriate criteria required under HHS regulations at 45 CFR 46.116(c) or (d) which require that the IRB find and document specific criteria when approving waiver or alteration of some or all of the required elements of informed consent. One example of this occurred in the expedited review and approval of IRB protocol #1105000388, titled "A Collaborative Evaluation of Charter School Performance in Rhode Island." The IRB waived the requirement to obtain informed consent but the specific criteria for the waiver were not documented. We determine that for some studies, informed consent was waived without documenting the appropriate criteria required in HHS regulations at 45 CFR 46.116(c) or (d).

Required Action: Please provide a plan to ensure that the IRB finds and documents specific criteria when approving waiver or alteration of some or all of the required elements of informed consent as required by HHS regulations at 45 CFR 46.116(c) and (d).

- 3) HHS regulations at 45 CFR 46.101(b) specify six categories of research that are exempt from the requirements of 45 CFR part 46. We determine that the institution applied an exemption to research activities that exceed these categories.
 - a. HHS regulations at 45 CFR 46.101(b)(4) exempt research that only involves the collection or study of existing data, documents, records, pathologic specimens, or diagnostic specimens provided specified conditions are met. We note that one of the conditions of exemption is that such research must be carried out in a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. IRB protocol #1104000372, "Effect of financial related factors on

medical students' specialty choice" was determined to be exempt under 45 CFR 46.101(b)(4). However, the research application indicates that personal identifiable information (including financial data) would be collected. We determine that this exemption was inappropriately applied because the research was carried out such that subjects could be identified.

Corrective Action: We acknowledge, per your email (dated August 29, 2011), that the IRB subsequently reviewed and approved the research.

- b. HHS regulations at 45 CFR 46.401(b) stipulate that the exemption at 45 CFR 46.101(b)(2) for research involving survey or interview procedures or observations of public behavior does not apply to research that involves children except for research involving observation of public behavior when the investigators do not participate in the activities being observed. IRB protocol #1103000358, "Social Circulation of Mediated Storytelling to Measure Speech in Moroccan Families" which, based on the study description and consent documents, involves children and was determined to be exempt under 45 CFR 46.101(b)(2). We determine that this exemption was inappropriately applied because the survey was administered to children.

Corrective Action: We acknowledge, per your August 30, 2011 email, that upon re-review of the protocol, you recognize this discrepancy and are currently working with the researcher to ensure that the research receives the appropriate modifications and IRB review.

Required Action: Please provide a plan to ensure that your institution appropriately applies exempt determinations to research activities specified in HHS regulations at 45 CFR 46.101(b).

B. Questions and concerns:

- 1) During our interviews with IRB members, we noted that at least one IRB member indicated that they did not recuse themselves from the deliberation and vote on studies on which they are a co-investigator. 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. We are concerned that IRB members may inappropriately participate in the review of protocols for which they have a conflicting interest, for example, by voting on protocols on which they are investigators. Please explain whether or not this is the case.
- 2) HHS regulations require that the IRB make specific findings to approve research involving prisoners. We are concerned that the IRB does not make the required findings or certify to the Secretary (through OHRP) that the IRB reviewed the research and made

the seven findings required by HHS regulations at 45 CFR 46.305-306, when reviewing prisoner research. For example, in IRB study #0512991954, “Group IPT for women prisoners with co-morbid substance use and depression,” we were unable to identify records indicating that the IRB made the seven additional findings required under HHS regulations at 45 CFR 46.305(a). Further, during our interviews of IRB members, questions about the specific findings that the IRB must make prior to approving such research were raised, and there appeared to be uncertainty about these regulatory requirements. Please explain whether the additional findings required under HHS regulations at 45 CFR 46.305(a) are made by the IRB, and whether Brown certifies to the Secretary (through OHRP) that the IRB made those findings as required by the regulations (45 CFR 46.305(c) and 46.306(a)(1)). For your information, “OHRP Guidance on the Involvement of Prisoners in Research,” is available on our website at <http://www.hhs.gov/ohrp/policy/prisoner.html>.

- 3) Based on our review of IRB records and meeting minutes, we are concerned that the convened IRB approves research when additional information is needed to make determinations required under HHS regulations at 45 CFR 46.111. The following are examples of studies where it appears that the convened IRB should have reviewed the additional information prior to granting approval:
- IRB #1105000390, “Developing an HIV Prevention Program for High Risk Couples”: The IRB approved this research contingent on receiving additional information about the rationale for the use of a mini mental exam and clarification regarding at what point or score would a participant be excluded. The investigator provided the information requested and the response was reviewed and approved by an expedited reviewer. The convened IRB did not see the additional information. It is not clear why the convened IRB did not need to see the additional information to make the appropriate determinations required under 111(a)(2) regarding risks to subjects being reasonable in relation to anticipated benefits; and 111(a)(7) regarding provisions to protect the privacy of subjects and to maintain the confidentiality of data.
 - IRB #0805992497, “Contingency Management for Alcohol Abuse Using Transdermal Alcohol Detection”: The IRB approved this research contingent on a response to a request for “a safety plan for managing participants who present with acute withdrawal symptoms that would require medical intervention,” and concerns about “the possibility that it may be difficult for participants to remove the ankle bracelet in an emergency, and [the need for] a solution to this problem.” This research involves a vulnerable population and was determined by the IRB to be greater than minimal risk. The investigator provided the information requested and the response was reviewed and approved by an expedited reviewer. The convened IRB did not see the additional information. It is not clear why the IRB did not need this information to make the appropriate determinations required under 111(a)(1)

regarding risks to subjects being minimized, and 111(a)(6) regarding adequate provisions for monitoring the data collected to ensure the safety of subjects.

- IRB #1008000244, “Coping Long Term with Attempted Suicide – Adolescents”: The IRB approved the research contingent on receipt of clarifications regarding the inclusion criteria, specifically suicidal ideation vs. suicide attempts, and the deletion of the term “treatment” in the consent—to which the investigator disagreed and left the reference to treatment in the protocol and consent. This research involves a vulnerable population and was determined by the IRB to be greater than minimal risk. The investigator provided the information requested and the response was reviewed and approved by an expedited reviewer. The convened IRB did not see the additional information. It is not clear why the IRB did not need this information to make the appropriate determinations required under 111(a)(1) regarding risks to subjects being minimized, and 111(b) regarding additional safeguards for vulnerable subjects.
- IRB #0512991954, “Group IPT for Women Prisoners with Co-morbid Substance Use and Depression”: The IRB approved a modification (on November 14, 2006) to the inclusion criteria to include participants that completed an additional program, specifically to include individuals that graduated from the “PR” program. The IRB requested information on how these subjects would be identified and recruited and more information about a study instrument and how it would affect subjects. This research involves a vulnerable population and was determined by the IRB to be greater than minimal risk. The investigator provided the information requested and the response was reviewed and approved by an expedited reviewer. The convened IRB did not see the additional information. It is not clear why the IRB did not need this information to make the appropriate determinations required under 111(a)(7) regarding provisions to protect the privacy of subjects and to maintain the confidentiality of data; and 111(b) regarding additional safeguards for vulnerable subjects.

We are concerned that the IRB approves research contingent upon substantive modifications or clarifications that were directly relevant to the determinations required by the IRB under HHS regulations at 45 CFR 46.111 without requiring additional review by the convened IRB. Please explain why it was not necessary for the convened IRB to review the responses to their requests for more information.

Please provide us with responses to the above determinations, questions and concerns by January 13, 2011, including a corrective action plan for the determinations. If you identify any areas of noncompliance in reviewing the above concerns, please describe corrective actions that you have taken or plan to take to address the noncompliance.

Dr. Briant — Brown University
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If you have any questions, or if you need assistance in developing a corrective action plan, please feel free to contact us. We appreciate your institution's continued commitment to the protection of human research subjects.

Sincerely,

Lisa R. Buchanan, MAOM
Compliance Oversight Coordinator
Division of Compliance Oversight

cc:

Ms. Dorinda Williams, Human Protections Administrator
Dr. Regina White, Associate Vice President for Research Administration
Dr. Ronald Seifer, IRB Chairperson
Dr. Brandon Krupp, IRB Vice Chairperson
Dr. Margaret Hamburg, Commissioner, Food and Drug Administration
Dr. Joanne Less, Food and Drug Administration
Mr. Joseph Ellis, National Institutes of Health, Office of Extramural Research
Dr. Sherry Mills, National Institutes of Health