



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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January 29, 2010

Yonette F. Thomas, Ph.D.
Associate Vice President for Research Compliance
Howard University
2400 Sixth Street, NW
Washington, DC 20059

RE: Human Research Protections Under Federalwide Assurance FWA-891

Research Project: Genetics of Early-Onset Depression

Principal Investigator: William Lawson, MD

HHS Protocol Number: 5R01MH075131

Dear Dr. Thomas:

Thank you for your September 28 and November 23, 2009 reports submitted in response to our July 21, 2009 request that Howard University (HU) respond to questions and concerns regarding allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46).

A. Determinations regarding the above-referenced research made in our April 13, 2009 letter:

In our April 13, 2009 letter, we made the following determinations:

- (1) HHS regulations at 45 CFR 46.116 state that no investigator may involve a human being as a subject in research covered by the regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative, or the institutional review board (IRB) has appropriately waived the requirements to obtain informed consent. We determined that the investigator initiated human subject research without obtaining legally effective informed consent of subjects and without the IRB appropriately waiving these requirements. In specific, we noted that the protocol envisions that identifiable private information about the subjects may be obtained from family members for research purposes prior to obtaining informed consent, but we can find no

evidence that the HU IRB waived informed consent for these subjects to the obtaining of this information.

Corrective Action: We acknowledge that the HU IRB has reviewed a revised consent form which addresses requesting information from family members, and has waived informed consent for the preliminary collection of information about family members prior to contacting them. In addition, the HU IRB has instituted a process that links IRB meeting agendas and IRB actions to letters to principal investigators and principal investigator responses to the IRB. The signatory official attends each IRB meeting to ensure that fair and efficient reviews are conducted and that the IRB process and administrative processes are connected. In addition, the HU IRB files digital recordings of the meeting and IRB members submit their specific comments electronically when a review is complicated to ensure that the principal investigator receives the most accurate feedback.

Required Action: Please provide the minutes of the IRB meeting in which the revised consent form was approved.

- (2) HHS regulations at 45 CFR 46.116(a) require that when seeking informed consent specific information shall be provided to each subject unless the IRB approves a consent procedure which does not include, or which alters, some or all of the required basic elements of informed consent provided in accordance with 45 CFR 46.116 (c) or (d). We determined that the informed consent documents reviewed and approved by the IRB for this study failed to include a description of any reasonably foreseeable risks and discomforts as required by HHS regulations at 45 CFR 46.116(a)(2). We noted that the protocol states that there is a theoretical risk that subjects may be identified on the basis of DNA information and that the informed consent document “notifies subjects of this theoretical risk as suggested by NIMH.” In addition, the protocol indicates that one of the risks of the research is violation of confidentiality which could be embarrassing to subjects and their relatives or could damage a subject’s reputation. We could not locate this information in the informed consent document.

Corrective Action: We acknowledge that the HU IRB has reviewed a revised consent form which addresses these risks.

Required Action: Please provide the minutes of the IRB meeting in which the revised consent form was approved.

- (3) We determined that HU did not have written IRB 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 need verification from sources other than the investigators that no material changes have occurred since previous IRB review. OHRP noted that the written procedures did state that such verification will occur, but did not state how projects needing such verification will be identified.

Corrective Action: We acknowledge that HU has drafted a document entitled: “Institutional Review Board: Research’s [sic] Guide.”

Required Action: By March 12, 2010, please provide us with a copy of the document “Institutional Review Board: Research’s [sic] Guide.”

B. Additional determinations regarding the above-referenced research

Based on our review of your May 21 and September 28, 2009 reports, we have the following additional determination:

In our February 5, 2009 letter to you, we outlined three allegations related to the above-referenced research.

- (a) Failure to report unanticipated problems involving risks to subjects or others to OHRP, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5). In specific, the complainant alleged that a research assistant for the above-referenced study obtained personal information about a subject in the study and harassed her by phone; in addition the research assistant shared identifiable private information about the subject to persons not associated with the research.
- (b) Changes to research were initiated without IRB review and approval, in contravention of HHS regulations at 45 CFR 46.103(b)(4)(iii). In specific, the complainant alleged that the research assistant for the above-referenced study did not have proper training or supervision.
- (c) That the institution failed to retain records relating to research for at least 3 years after completion of the research, in contravention of HHS regulations at 45 CFR 46.115(b). In specific, the complainant alleged that information a subject provided to Howard University for research purposes was destroyed prior to such a date.

We determine that the unanticipated problem involving risks to subjects or others described in (a) above was not reported to OHRP, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

Corrective Action: We acknowledge your statements that HU’s corrective action plan will incorporate the ongoing HIPAA training currently provided by HU and reinforced compliance training provided by the Office of the Vice President for Research and Compliance. This compliance training will address participant protection-specific issues, reporting responsibilities, and sanctions for noncompliance. The training will also include a review of all applicable policies, procedures, and processes, and identify and address any gaps that allowed this unanticipated problem, and failure to report to OHRP, to occur. The anticipated implementation of this training is April 2010. We further acknowledge that the IRB is paying particular attention to this and similar issues, and the chairperson of the HU IRB has incorporated this example into training delivered to the HU community on

November 9, 2009. We determine that these corrective actions adequately address the above determination.

We acknowledge your statements that the research assistant in question received training to conduct screening interviews, which continued throughout his employment on this study, and that when the principal investigator was informed of the complaint against him on June 9, 2006, the research assistant in question was instructed that he must have no further contact with research subjects pending the outcome of the investigation, and the principal investigator took steps to secure the complainant's identity and remove her from the contact list. The IRB was notified of the complaint on September 8, 2006. The research assistant in question was officially terminated from HU on December 6, 2006. We also note that the study is still ongoing and that all records required by HHS regulations at 45 CFR 46.115(b) appear to have been maintained.

As a result, we determine that the allegations that the research assistant for the above-referenced study did not have proper training or supervision and that the institution failed to retain records relating to this research for at least 3 years after completion of the research are unproven. [However, we note that there was a failure to retain research records in others studies (see paragraph C(4) below).]

C. Additional determinations regarding your institution's system for protecting human subjects

- (1) In order to approve research, the IRB must determine that the research satisfies the criteria for approval under HHS regulations at 45 CFR 46.111. The minutes of several HU IRB meetings indicate that numerous protocols were approved even though the IRB had substantive questions about how the research was conducted, which information it appears the IRB would have needed in order to make the determinations required under HHS regulations at 45 CFR 46.111. In specific, we determine that the following protocols were approved at the following IRB meetings in apparent absence of this information:
 - (a) May 9, 2007: #316. IRB-07-CAS-10, although the IRB requested information about the number of subjects to be recruited, and where subjects are coming from.
 - (b) August 16, 2006: #42. IRB-06-MED-36, although the IRB requested information about which studies needed to be performed as regular exam versus this study, who pays for the tests, and whether or not there is any radiation from the topography.
 - (c) May 24, 2006: #458. IRB-05-DEN-17, although the IRB requested information about how subjects will be identified and recruited, and what is the alternative to participation; #470. IRB-06-MED-21, although the IRB requested information about how many subjects would be recruited at HU, how will students be identified and recruited, will there be an agreement to allow further use of DNA samples, and noted that the consent form was incomplete; #474. IRB-06-CAS-03, although the IRB

- requested information about which school the study would be conducted at, and information about recruitment methods.
- (d) January 11, 2006: #193. IRB-05-SW-10, although the IRB requested information about clarification of some subjects being medicated, what happens if someone is really upset, inclusion and exclusion criteria, and where the study will be conducted; #207-IRB-06-PED-01, although the IRB requested information about whether or not data will be kept confidential; #210. IRB-06-GSAS-01, although the IRB requested information about recruitment methods, missing parental consent, child assent and teacher consent forms, how classes will be selected, and how teachers are involved.
- (e) December 14, 2005: #156. IRB-99-MED-09, although the IRB requested information about how subjects will be identified and recruited and length of the procedures; #186. IRB-05-DEN-24, although the IRB requested information about the method of delivering the documents, recruitment, time frame, and where the subjects are coming from.

Corrective Action: We acknowledge that the HU IRB has instituted a process that links IRB meeting agendas and IRB actions to letters to principal investigators and principal investigator responses to the IRB. The signatory official attends each IRB meeting to ensure that fair and efficient reviews are conducted and that the IRB process and administrative processes are connected. In addition, the HU IRB files digital recordings of the meeting and IRB members submit their specific comments electronically when a review is complicated to ensure that the principal investigator receives the most accurate feedback. We note that the proposed corrective actions do not directly address the regulatory noncompliance found by OHRP.

Required Action: By March 12, 2010, please provide corrective actions to ensure that, when the IRB at a convened meeting requests information that the IRB would need in order to make the determinations required under HHS regulations at 45 CFR 46.111, the protocol is not approved until the information is reviewed and approved by the IRB at a subsequent convened meeting or by an expedited review procedure, if appropriate.

- (2) 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, but 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. We determine that the IRB failed to conduct continuing review of research at least once per year and that research was conducted after expiration. In specific, the following protocols lapsed prior to IRB review and approval at the following meetings:

- (a) September 23, 2009: IRB-08-MED-13; IRB-99-CC-06; IRB-08-MED-35; IRB-08-SW01.

- (b) May 9, 2007: WAS 301-1: #154-2. IRB-05-MED-45; #262-2. IRB-05-CC-02; #308. IRB-04-MED-16.
- (c) August 16, 2006: #35. IRB-04-MED-21.
- (d) May 24, 2006: #461. IRB-04-MED-13; #462. IRB-04-MED-06; #466. IRB-05-GSAS-09; #468. IRB-05-CC-02; IRB-05-MED-13.
- (e) January 11, 2006: #196. IRB-03-MED-15; #201. IRB-00-DEN-04; #202. IRB-03-MED-07.
- (f) December 14, 2005: #152-2. IRB-99-MED-09.
- (g) We also note that protocol #313. IRB-06-CAS-05 was approved at continuing review on May 9, 2007, but was given an expiration date of August 6, 2008, more than one year after approval.

Corrective Action: We acknowledge your statement that the HU IRB has implemented a new process in which investigators are instructed to submit renewal requests at least 30 days prior to the expiration date and that any requests submitted thereafter will be denied unless an arrangement is made to expedite or administratively review the protocol. Please note that HHS regulations at 45 CFR 46.110(b)(1) limit the use of expedited review procedures for initial or continuing review to specific research categories published in the Federal Register at 63 FR 60364--60367 (see <http://www.dhhs.gov/ohrp/humansubjects/guidance/expedited98.htm>) when the research is determined to involve no more than minimal risk, and that there is no mechanism in the regulations for “administrative review.” These corrective actions does not directly address the regulatory noncompliance found by OHRP.

Required Action: By March 12, 2010, please provide corrective actions to ensure that when a research protocol has expired, investigators are notified that all activities involving human subjects research (including analysis of identifiable private information) must stop, unless the IRB determines that it is in the best interest of subjects to for the research activities to continue. Please also provide corrective actions to ensure that that expiration dates for IRB-approved research are not assigned for more than one year after IRB approval.

- (3) We determine that a suspension or termination of IRB approval was not reported to OHRP as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5). The August 2008 FDA inspection of the HU IRB revealed that one study, IRB-03-SCD-02 directed by PI Onyinye Onekwere, M.D., M.S, was suspended from 3/16/2007 until 7/18/2007. This was never reported to our office.

Corrective Action: We acknowledge your statement that staff and IRB members have been re-trained on the rule that all suspensions in protocols and recruitment must be reported to OHRP, and that you are responsible for enforcing and maintaining these procedures. We determine that this corrective action adequately addresses our determination.

- (4) HHS regulations at 45 CFR 46.115(b) require that IRB records be retained for at least 3 years, and records relating to research which is conducted be retained for at least 3 years after completion of the research. All records must be accessible for inspection and copying by authorized representatives of HHS at reasonable times and in a reasonable manner. We determine that HU failed to retain IRB records and records relating to research for at least 3 years after completion of the research at that study site for protocols IRB-04-MED-16, IRB-06-CAS-03, and nIRB-06-GSAS-01.

Corrective Action: We acknowledge your statement that each protocol is now scanned and saved to an external hard drive. This corrective action does not directly address the regulatory noncompliance found by OHRP.

Required Action: By March 12, 2010, please provide a corrective action to ensure that **all** records required by HHS regulations at 45 CFR 46.115(b) are retained for at least 3 years, and records relating to research which is conducted are retained for at least 3 years after completion of the research.

Please provide us with responses to the above determinations by March 12, 2010, including a corrective action plan for the determinations of noncompliance. Feel free to contact me if you would like guidance in developing a corrective action plan.

D. Recommendations

We make the following recommendation regarding HU's human subject protection program:

We note that the protocol includes provisions for waiver of documentation of informed consent ("oral/verbal consent"); however, the protocol outlines the conditions for approval of waiver of informed consent, not waiver of the requirements for documenting informed consent with a signed consent form. Please note that waiver of documentation of informed consent is not the same as waiver of informed consent, and has different requirements (see HHS regulations at 45 CFR 46.117(c))

We appreciate 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,

Kristina C. Borrer, Ph.D.
Director, Division of Compliance Oversight

cc: Dr. Charles P. Mouton, Professor & Chairman, Dept. of Community & Family
Medicine, HU

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Yonette F. Thomas, Ph.D.-- Howard University

January 29, 2010

Dr. Anthony K. Wutoh, IRB Chair, HU

Dr. William Lawson, HU

Dr. Sherry Mills, National Institutes of Health

Mr. Joseph Ellis, National Institutes of Health

Dr. Thomas R. Insel, Director, National Institute of Mental Health