DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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December 17, 2007

Peter J. Deckers, M.D.
Executive Vice President for Heath Affairs
University of Connecticut Health Center
263 Farmington Avenue
Farmington, CT 06030-3826

RE: Human Research Subject Protections Under Federalwide Assurance FWA-6064

Research Project:	Effects of Aripiprazole on Subjective and Physiological Responses to Alcohol
Principal Investigator:	Henry Kranzler, M.D.
Project Number:	GCRC #536 (MO1 RR06192); IRB 04-108
Research Project:	Targeted Naltrexone for Problem Drinkers
Principal Investigator:	Henry Kranzler, M.D.
Project Number:	GCRC #495; IRB 03-107
Research Project:	Sertraline Pharmacotherapy for Alcoholism Subtypes
Principal Investigator:	Henry Kranzler, M.D.
Project Number:	GCRC #531; IRB 03-225

Dear Dr. Deckers:

The Office for Human Research Protections (OHRP) has reviewed the University of Connecticut Health Center (UCHC) October 1, 2007 report in response to the OHRP August 9, 2007 letter regarding research conducted under the above-referenced research projects.

In its letter dated August 9, 2007, OHRP made the following determinations:

(1) OHRP found that the UCHC Institutional Review Board (IRB) approved consent forms for IRB 03-107 that failed to include the following informed consent elements specific to DNA testing as required by Department of Health and Human Services (HHS) regulations at 45 CFR 46.116(a):

(a) Section 46.116(a)(1): An explanation of the purposes of the DNA testing aspects of the research and a complete description of the DNA tests to be run on the collected blood.

(b) Section 46.116(a)(2): A description of any reasonably foreseeable risks and discomforts to the subjects regarding DNA testing.

(c) Section 46.116(a)(3): A description of any benefits to the subject or others that may reasonably be expected from the DNA testing.

(d) Section 46.116(a)(5): A statement describing the extent, if any, to which confidentiality of records/samples identifying the subject will be maintained.

Corrective Action: OHRP acknowledges that the UCHC Human Subjects Protection Office (HSPO) has revised its informed consent form checklist to ensure that DNA testing issues are more thoroughly and specifically addressed in consent forms. The checklist has been revised to provide clear direction for the inclusion of the following elements specific to DNA testing:

- An explanation of the purpose(s) of the DNA testing aspects of the research and a description of the DNA tests to be run on the collected sample;
- A description of any foreseeable risks and discomforts to the subjects regarding DNA testing;
- A description of any benefits to the subject or others that may reasonably be expected from the DNA testing;
- A statement describing the extent, if any, to which the confidentiality of these records/samples identifying the subject will be maintained.

OHRP further acknowledges that the UCHC research community and IRB members and staff have been informed of this issue via a broadcast message and a HSPO newsletter. Lastly, OHRP acknowledges that investigators with existing studies have been directed to review their consent forms and, if needed, to submit a modification request to ensure that the consent forms adequately address the above-referenced items. These corrective actions appear to be adequate under the terms of the UCHC FWA.

OHRP makes the following additional determinations:

(2) OHRP finds that the discovery regarding UCHC IRB-approved protocols involving unqualified research team personnel did constitute an unanticipated problem involving risks to subjects and that UCHC failed to promptly report this unanticipated problem involving risks to subjects to the UCHC IRB, appropriate UCHC institutional officials, the department or agency head and OHRP as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5). This finding is based on the following statement in the October 1, 2007 UCHC report: "We recognize that, … by

having patients medically evaluated by unlicensed physicians, the PI did put patients at risk."

Corrective Action: OHRP acknowledges that the UCHC HSPO has been proactive in educating investigators about the requirement to report noncompliance and unanticipated problems to the IRB. In addition, OHRP acknowledges that UCHC now uses a problem report form for filing such information with the UCHC IRB. This corrective action appears to be adequate under the terms of the UCHC FWA.

(3) OHRP finds that the UCHC IRB approved the DNA testing procedures associated with IRB 03-225 and 04-108 without first reviewing sufficient information regarding the DNA testing procedures that was needed to make the determinations under HHS regulations at 45 CFR 46.111.

(4) OHRP finds that the UCHC IRB-approved consent forms for IRB 03-225 failed to include the following informed consent elements specific to DNA testing as required by 45 CFR 46.116(a):

(a) Section 46.116(a)(2): A description of any reasonably foreseeable risks and discomforts to the subjects regarding DNA testing.

(b) Section 46.116(a)(3): A description of any benefits to the subject or others that may reasonably be expected from the DNA testing.

Corrective Action: OHRP notes that the following corrective actions have been taken to address this finding as well as finding (3) above:

(a) The UCHC HSPO has revised the informed consent form checklist to ensure that DNA testing issues are more thoroughly and specifically addressed in consent forms;

(b) The UCHC HSPO has revised the work sheet used by IRB reviewers to ensure that all protocols involving DNA testing adequately address such testing;

(c) The UCHC research community and IRB members and staff have been informed of this issue via a broadcast message and a HSPO newsletter; and

(d) Investigators with existing studies involving DNA testing have been directed to review their protocols and consent forms and, if needed, submit a request for modification to the IRB.

These corrective actions appear to be adequate under the terms of the UCHC FWA.

(5) HHS regulations at 45 CFR 46.103(b) and 46.109(a) require that an IRB review and approve all non-exempt human subject research covered by an institution's assurance.

The creation of a recruitment database and the anticipated use of the information contained in that database to recruit subjects for future research studies constitutes research as defined in HHS regulations at 45 CFR 46.102(d). If such a database in fact exists, and the database contains identifiable private information, the database involves human subjects, as defined by HHS regulations at 45 CFR 46.102(f). OHRP finds that Dr. Kranzler conducted non-exempt human subjects research without prior IRB review and approval when he created a recruitment database containing identifiable private information, i.e., names, contact information and health information, from IRB #04-108 phone excludes.[1]

Corrective Action: OHRP notes the following:

(a) UCHC policies require that the IRB review and approve the creation of a research registry and/or bank as well as projects that subsequently make use of the identifiable information within such a registry/bank;

(b) The principal investigator (PI) has been instructed that the existing data collected from phone excludes can no longer be used for any purpose other than a general mailing list containing only names and addresses; identifiable private information must be removed;

(c) The PI has been instructed that in order to maintain any private identifiable information the PI must obtain approval for a registry/repository prior to placing information in the registry/repository and that each subject must provide consent and authorization for participation in the registry/repository;

(d) The policy regarding the requirement to obtain approval for a registry and/or bank has been reiterated in the broadcast message and newsletter; and

(e) The language on the third page of the template research HIPAA authorization document that led to this misunderstanding has been revised as follows to reflect clearly that subjects are only consenting to have their names and addresses added to a general mailing list:

> " _____ You give permission to *[insert research(s) name]* or *[his, her, their]* designated staff to add your name and address to a mailing list to receive information about other studies we may conduct."

Required Action: Given the potential systemic nature of this finding, please explain what actions, if any, the UCHC IRB plans to take regarding other investigators who may have engaged in non-exempt human subject research, i.e., created a human

[1] OHRP acknowledges that "The PI has confirmed that no identifiable data has been collected for registry or future contact purposes for study #03-107 or #03-225."

subjects participant registry containing identifiable private information, without IRB review and approval.

(6) As stated above, HHS regulations at 45 CFR 46.103(b) and 46.109(a) require that an IRB review and approve all non-exempt human subject research covered by an institution's assurance. The creation of a repository and the anticipated use of the biological specimens maintained in the repository for future research studies constitutes research as defined in HHS regulations at 45 CFR 46.102(d). If such a research repository exists, and the repository contains biological specimens with identifiable private information, the repository would involve human subjects, as defined by HHS regulations at 45 CFR 46.102(f). OHRP finds that Dr. Kranzler conducted non-exempt human subjects research, i.e., establishment of a blood bank repository containing biological specimens with identifiable private information, without prior IRB review and approval.

Corrective Action: OHRP acknowledges that Dr. Kranzler will be submitting a proposal for a blood bank to the IRB and that upon approval of the bank, the principal investigator will obtain separate consent from subjects, i.e., consent for participation in a specific study and consent for samples to be added to the bank. OHRP further acknowledges that the UCHC research community and IRB members and staff have been informed about the requirement to obtain IRB approval for a registry and or bank. Lastly, OHRP notes that the principal investigator has been informed that existing identifiable samples that remain from previously approved studies must be stripped of identifiers or discarded in an appropriate manner.

Required Action: Given the potential systemic nature of this finding, please explain what actions, if any, the UCHC IRB plans to take regarding other investigators who may have engaged in non-exempt human subject research, i.e., created a research repository containing identifiable private information, without IRB prior review and approval.

OHRP has the following questions and concerns:

(7)[Redacted]

[Redacted]

[Redacted]

(8) [Redacted]

(9) [Redacted]

OHRP acknowledges all of the remaining UCHC responses that are not specifically addressed above.

Please submit your response to the findings, questions and concerns noted above so that OHRP receives them no later than February 8, 2008. If during your review you identify additional areas of noncompliance with HHS regulations for the protection of human subjects, please provide corrective action plans that have been or will be implemented to address the noncompliance.

OHRP appreciates your institution's continued commitment to the protection of human research subjects. Do not hesitate to contact OHRP if you should have any questions regarding this matter.

Sincerely,

Lisa A. Rooney, J.D.
Compliance Oversight Coordinator

cc: Dr. Richard H. Simon, Director, Human Subjects Protection Office, UCHC
Ms. Judi Kulko, IRB chairperson, UCHC IRB #1
Dr. Ronald M. Kadden, IRB chairperson, UCHC IRB #2
Dr. Mahlon Hale, IRB chairperson, UCHC IRB#1 - Panel 03
Dr. Nancy R. Rodrigues, IRB chairperson, University of Connecticut, Storrs IRB #1
Dr. Amira Pierucci-Lagha, UCHC
Dr. Henry Kranzler, UCHC
Ms. Sherry Mills, NIH Office of Extramural Research
Mr. Joe Ellis, NIH Office of Extramural Research
Dr. Andrew C. von Eschenbach, Commissioner, FDA
Dr. Joanne R. Less, OHPR
Dr. Ivor Pritchard, OHRP
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Mr. Barry Bowman, OHRP