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September 2, 2009

James C. Walker, PhD
Interim Associate Vice President for Research
The University of Iowa
200 Gilmore Hall
Iowa City, IA 52242-1101

RE: Human Research Protections Under Federalwide Assurance FWA-3007

**Research Project: PET Studies of Cerebral Blood Flow in Relationship to
Cognition, Emotion, and Behavior**

Principal Investigator: Nancy C. Andreasen, M.D.

Dear Dr. Walker:

Thank you for your January 14, 2009 report in response to our December 8, 2008 request that the University of Iowa (UI) investigate allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR Part 46) involving the above-referenced research.

Based upon your December 8, 2008 report we make the following determinations regarding this research study:

A. Determinations regarding the above-referenced research

- (1) HHS regulations at 45 CFR 46.116 require that investigators obtain the legally effective informed consent of a subject or of the subject's legally authorized representative prior to involving him or her in HHS-conducted or supported research. A subject in the above-referenced research funded by the National Institutes of Health (NIH) who was admitted to the University of Iowa psychiatric hospital on April 3, 1994 (hereinafter referred to as "Subject") alleged that she was not competent to give informed consent for the above-referenced schizophrenia research project, and that consent was not obtained from a legally authorized representative.

Given the facts at our disposal, we determine that the allegation that Subject was not competent to provide her own informed consent to participate in the above-referenced research study is unproven. The NIH funding application for this research states that subjects are to be evaluated with a comprehensive assessment battery including structured interviews, family history, and neuropsychological tests. UI's report in response to OHRP's request for investigation stated that Subject was admitted to UI's psychiatry inpatient service under a voluntary consent for admission and was not on any medication. Her parents accompanied her but did not act as her legally authorized representative in any matters related to admission. Following her admission she was screened by a research team at UI's Mental Health Clinical Research Center (MHCRC), an inpatient research unit dedicated to research studies of schizophrenia. The screening interview was designed to obtain a diagnostic impression, educate subjects and families about the risks and benefits of research studies, and evaluate subjects' ability to give informed consent. After passing this screening and indicating a willingness to participate in research studies, per MHCRC procedure, Subject's competence was further evaluated at a staff meeting of ten research physicians who concluded that she was competent to provide informed consent to participate in schizophrenia research. According to UI, a staff note about Subject written by the physician in charge of MHCRC states: "pt cooperative, thoughts goal directed, mood neutral, elaborate delusional system, cognitively intact." According to UI nursing notes from April 4, 1994, the day following Subject's admission to UI's psychiatry inpatient service, Subject watched a video about PET and discussed PET screening with nurses. Subject subsequently signed a consent form to participate in the above-referenced research on that date. Based on these facts, we conclude that the investigators took appropriate steps to obtain the legally effective informed consent of Subject before involving her in the research, as required by 45 CFR 46.116.

- (2) It was alleged that investigators failed to seek informed consent from Subject to participate in the above-referenced research under circumstances that minimized the possibility of coercion or undue influence, as required by HHS regulations at 45 CFR 46.116. From the information provided to us by UI, we note that Subject came to UI's psychiatric facility voluntarily. She was not offered any compensation to participate in the research, and the consent form she signed stated that there was no predictable benefit to her from participating. Subject's mother was present when Subject was screened for participation in research, and Subject's mother was supportive of Subject's enrollment in the MHCRC research program. Given these facts provided by UI, we determine that this allegation is unproven.

- (3) It was alleged that the investigators failed to provide Subject with a copy of the consent document for the above-referenced research, as required by HHS regulations at 45 CFR 46.117(a). From the UI report, we understand that it was standard practice at MHCRC to make three copies of consent forms, placing one in subjects' clinical charts, giving one to the primary nurse for a working file, and giving one to the subject. UI currently retains the copy that was placed in Subject's clinical record when she signed the consent document on April 4, 1994. Moreover, UI provided a copy of the consent document to Subject when Subject requested one in 2008, during the course of this investigation. However, Subject's mother informed us that she does not specifically recall that either she or her daughter received a copy of the consent document when Subject signed it as an inpatient at UI. Given the facts at our disposal, we determine that there is no proven violation of the regulations regarding this allegation.
- (4) HHS regulations at 45 CFR 46.109 require that continuing review of research be conducted by the institutional review board (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 during the period from 1991-1999 when the above-referenced research was conducted at UI, continuing review for the above-referenced research did not always occur at least once per year. For example, the first continuing review occurred on February 27, 1992 and subsequent continuing reviews apparently occurred on April 1, 1993, May 12, 1994, May 10, 1995, June 27, 1996, June 26, 1997, July 9, 1998, and July 15, 1999.

Corrective Action: We understand that UI now utilizes an electronic application and database system, HawkIRB, using smart-form technology. When a research project is due for continuing review, HawkIRB automatically e-mails the principal investigator (PI) and specified members of the research team notifying them of the upcoming final submission date for review. The first e-mail is sent 30 days prior to the last day an application may be submitted, to allow time to review prior to expiration. Additional e-mails are sent at 14, 7 and 1 day prior to this final submission date. On the final submission date, if no continuing review application has been received, notification is sent to the PI and all research team members indicating that UI IRB approval will lapse as of 12:01 a.m. on the expiration date and no further research activity may occur on

or after that date. This corrective action adequately addresses our determination.

B. OHRP Guidance

We note that two days after Subject enrolled in the above research, on April 6, 1994, Subject's mother signed an information sheet for a companion study titled "Phenomenology and Classification of Schizophrenia (Longitudinal Study)" and agreed to provide information on symptoms or personality characteristics of her daughter and any associated changes over an eight year period. The information sheet stated:

Although the only direct benefit to you will be monetary compensation for your time (\$30 per interview), your relative/friend will receive close monitoring of his illness which would be basically impossible in an ordinary clinic or hospital setting.

Informing potential subjects who are family members of patients recently diagnosed with mental illness that it "would be basically impossible" [to replicate MHCRC's] "close monitoring" of their disease in "an ordinary clinic or hospital setting" could have resulted in possible coercion or undue influence during the consent process. We note that under HHS regulations at 45 CFR 46.116, investigators must seek consent under circumstances that minimize the possibility of coercion or undue influence. We recommend that the UI IRB, when reviewing research in the future, take steps to ensure that the informed consent documents it approves do not include similar language.

At this time, there should be no need for further involvement by our office in this matter. Please notify us if you identify new information which might alter this determination.

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,

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

cc:
Ms. Michele Countryman, IRB Administrator, The University of Iowa
Ms. Martha F. Jones, IRB Chairperson, The University of Iowa

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James C. Walker, PhD-- The University of Iowa
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