DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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Charles F. Zukoski
Vice Chancellor for Research
University of Illinois
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Fourth Floor Swanlund Building
601 East John Street
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RE: Human Research Subject Protections Under Federalwide Assurance FWA 8584

Dear Dr. Zukoski,

As you know, the Office for Human Research Protections (OHRP) conducted an on-site evaluation of the human subject protections system at the University of Illinois at Urbana/Champaign (UIUC) from September 19 to September 21, 2006. The evaluation, conducted by four OHRP staff and with the assistance of one expert consultant, included meetings with senior institutional officials, the chairperson of the UIUC Institutional Review Board (IRB), IRB members, IRB administrative staff, and six research investigators. The evaluation involved the review of IRB files for approximately 40 protocols, as well as the minutes of numerous IRB meetings.

In the course of the OHRP review, the IRB chairperson, IRB members, and IRB administrative staff displayed a sincere commitment to the protection of human subjects. Furthermore, the volume of research reviewed and the amount of time and effort devoted to IRB activities by the IRB chairpersons and staff indicate great dedication to the mission of the IRB. The IRB administrator and staff were very helpful and accommodating to OHRP during the site visit.

OHRP notes that there appears to have been substantial improvements in the operations of the IRB over the past 1-2 years. These improvements were commented on by many individuals interviewed during the course of the visit, including IRB members and research investigators.

Findings

Based on the review of materials submitted in UIUC's August 27 and September 8, 2006 correspondence, as well as interviews and materials reviewed during its site visit, OHRP makes the following determinations:

(1) The Department of Health and Human Services (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. OHRP finds that the IRB failed to conduct continuing review of some research at least once per year. OHRP notes that the following protocols include examples where IRB review was not conducted at least once per year (Protocols 03144, 00053, and 05448).

The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval. Additionally, where the convened IRB specifies conditions for approval of a protocol that are to be verified as being satisfied by the IRB Chair or another IRB member designated by the Chair, continuing review must occur no later than one year after the date the protocol was reviewed by the convened IRB, not on the anniversary of the date the IRB Chair or his or her designee verifies that IRB-specified conditions for approval have been satisfied. OHRP notes that the IRB consistently assigns an anniversary date that is one year from the date that an IRB member verifies that contingencies have been satisfied, rather than using the date of the convened meeting at which approval occurs.

The OHRP guidance document entitled "Guidance on Continuing Review," dated July 11, 2002, clearly sets forth OHRP's position on this issue. Please see the section entitled "How is the continuing review date determined?" at http://www.hhs.gov/ohrp/humansubjects/guidance/contrev2002.htm.

The IRB and investigators must plan ahead to meet required continuing review dates. If an investigator has failed to provide continuing review information to the IRB or the IRB has not reviewed and approved a research study by the continuing review date specified by the IRB, the research must stop, unless the IRB finds that it is in the best interest of currently enrolled subjects to continue participating in the research interventions or interactions. The IRB may consider a request for continued participation of all subjects currently enrolled. Enrollment of new subjects cannot occur after the expiration of IRB approval.

(2) HHS regulations at 45 CFR 46.408(b) require that the IRB shall determine, in accordance with and to the extent that consent is required by 45 CFR 46.116, that adequate provisions are made for soliciting the permission of each child's parents or guardian. OHRP finds that the investigator initiated human subject research in study 97004 without obtaining the parental permission for the subjects enrolled in the

research. In particular, OHRP found that this protocol involved a "passive consent" procedure which did not allow for parental permission to be obtained.

In addition, in the review of the study file, OHRP found no evidence that the IRB made the four specific determinations required for approving a waiver or alteration of some or all of the required elements of informed consent required under 45 CFR 46.116(d).

(3) HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5) require reporting to the IRB, appropriate institutional officials, the department or agency head, and OHRP of (i) any unanticipated problem involving risks to subjects or others; (ii) any serious or continuing noncompliance; or (iii) any suspension or termination of IRB approval. OHRP notes that for protocol 97004, noted above, parents of certain subjects did not receive informed consent documents as part of the "passive consent"and did not have an opportunity to give permission for the enrollment of their children in the research. Although this was recognized by the investigator to be a serious problem and reported to the IRB and others in the institution, OHRP finds that this serious noncompliance was not reported to OHRP.

(4) OHRP finds that the informed consent documents reviewed and approved by the IRB for protocol 02187 failed to include a complete description of the procedures to be followed, as required by HHS regulations at 45 CFR 46.116(a). In specific, the IRB-approved informed consent document did not provide a description of the EROS procedure.

(5) HHS regulations at 45 CFR 46.116 require that informed consent information be in language understandable to the subject or the subject's legally authorized representative. OHRP finds that the informed consent document approved by the IRB for the two studies below included examples of complex language that would not be understandable to all subjects. In specific, OHRP notes that (i) the informed consent document for protocol 06742 used the term "transvaginal ultrasound" without any further description; and (ii) the informed consent document for protocol 06580 mentioned the use of "ergonomic wearable products" when enrolling subjects who were from a nursing home population.

Required Action: UIUC must develop a satisfactory corrective action plan to address the above determinations.

OHRP is available to assist UIUC in the development and implementation of these corrective action plans. Do not hesitate to contact me should you have any questions.

Questions and Concerns

At this time OHRP has the following additional questions and concerns:

(6) [Redacted]

(7) [Redacted]

(8) [Redacted]

(9) [Redacted]

Guidance

OHRP would like to provide UIUC with the following guidance:

(11) OHRP recommends that each revision to a research protocol be incorporated into the written protocol. This practice ensures that there is only one complete protocol with the revision dates noted on each revised page and the first page of the protocol itself. This procedure is consistent with the procedure used for revised and approved informed consent documents which then supersede the previous one.

(12) OHRP recommends that IRBs exercise oversight over the operation of student "human subject pools." When collecting private identifiable information, subject pool procedures must be in accordance with HHS regulations and must ensure (a) that consent for participation is sought only under circumstances which minimize the possibility of coercion or undue influence, and (b) that genuinely equivalent alternatives to participation are available.

(13) As noted above, HHS regulations at 45 CFR 46.116(d) require that the IRB make and document four findings when approving a consent procedure which does not include, or which alters, some or all of the required elements of informed consent or when waiving the requirement to obtain informed consent. OHRP recommends that when approving such a waiver for research reviewed by the convened IRB, these findings be documented in the IRB records, including *protocol-specific* information justifying each IRB finding.

Similarly, where HHS regulations require specific findings on the part of the IRB, such as (a) approving a procedure which waives the requirement for obtaining a signed consent form [see 45 CFR 46.117(c)]; (b) approving research involving pregnant women, human fetuses, or neonates (see 45 CFR 46.204-207); (c) approving research involving prisoners (see 45 CFR 46.305-306); or (d) approving research involving children (see 45 CFR 46.404-407), the IRB should document such findings. OHRP recommends that for research approved by the convened IRB, all required findings be fully documented in the IRB records, including *protocol-specific* information justifying each IRB finding.

For research reviewed under an expedited review procedure, these findings should be documented by the IRB chairperson or other designated reviewer elsewhere in the IRB record.

Please forward the corrective action plan and responses to the above questions and concerns so that OHRP receives it no later than November 15, 2006.

OHRP appreciates 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,

Patrick J. McNeilly, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Melanie Loots, Associate Vice Chancellor for Research, UIUC
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