DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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June 29, 2005

Lewis J. Smith, M.D.
Acting Vice President for Research
Northwestern University
710 N. Lake Shore Drive
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RE: Human Research Subject Protections Under Federalwide Assurance FWA-1549

Dear Dr. Smith:

As you know, the Office for Human Research Protections (OHRP) conducted an on-site evaluation of human subject protection procedures at Northwestern University (NU) from May 10-12, 2005. The evaluation was conducted by four OHRP staff members with the assistance of two expert consultants, and included meetings with institutional officials; the institutional review board (IRB) chairs, members, and administrative staff of NU IRB Panels A-E; and a limited number of principal investigators who submit protocols to the IRBs. OHRP reviewed IRB files for approximately 35 open protocols, 20 exempt protocols, and the minutes of a number of IRB meetings held from 2003-2005.

In the course of the OHRP review, the IRB chairs, members, and administrative staff displayed an enthusiastic and sincere concern for, and commitment to, the protection of human subjects, and stated that they view themselves as providing a valuable service to subjects and the research community. Investigators demonstrated a culture of respect for the IRB process. The staff of the Office for the Protection of Research Subjects (OPRS) were helpful and accommodating to OHRP during the site visit.

OHRP acknowledges NU's proactive efforts in the past few years to increase research support services and facilities, to create a new Office of Research Integrity, and to initiate a Web-based system for research project submissions which should aid in both the documentation and the accuracy of IRB records.

OHRP Findings and Concerns Relative to Systemic Protections for Human Subjects

Based on its evaluation, OHRP makes the following determinations:

(1) The Department of Health and Human Services (HHS) regulations at 45 CFR 46.111 set forth the criteria that must be satisfied in order for the IRB to approve research. These criteria include, among other things, determinations by the IRB regarding risks, potential benefits, informed consent, and safeguards for human subjects. The IRB must ensure that these criteria are satisfied at the time of both initial and continuing review. OHRP finds that when reviewing the applications for research protocols #0108-015, #0221-016, #0390-020, #0390-021, and #0542-016, the NU IRBs appeared to lack sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. In addition, OHRP finds that the NU IRBs approved these research protocols contingent upon substantive modifications or clarifications that were directly pertinent to the determinations that the IRBs must make under 45 CFR 46.111, without requiring additional review by the convened IRBs.

(2) HHS regulations at 45 CFR 46.404-407 require specific findings on the part of the IRB for approval of research involving children. Based on discussions with IRB members and its review of IRB documents, OHRP finds little evidence that the NU IRBs consistently make the required findings when reviewing research involving children.

(3) HHS regulations at 45 CFR 46.204-205 state that pregnant women, fetuses, and neonates may be involved in research if certain conditions are met. Based on OHRP's discussions with IRB members and its review of IRB documents, OHRP finds little evidence that the NU IRBs consistently determine that the conditions are met when reviewing research involving these populations.

(4) HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5) and the NU FWA require that (i) unanticipated problems involving risks to subjects or others, (ii) any serious or continuing noncompliance with 45 CFR part 46 or the requirements or determinations of the IRB, and (iii) any suspension or termination of IRB approval be promptly reported to the IRB, appropriate institutional officials, the department or agency head, and OHRP. OHRP finds that unanticipated problems involving risks to subjects or others, serious or continuing noncompliance, and suspension of IRB approval were not reported to OHRP for research protocol #0947-004. Further, OHRP finds that for research protocols #0141-022, #0141-024, #0141-025, #0141-026, #0141-031, #0141-034, #0141-037, #0165-007, and #1279-005, NU failed to promptly report suspensions of IRB Panel D's approval to OHRP.

(5) HHS regulations at 45 CFR 46.304 require modification of IRB membership for review of research involving prisoners. For example, at least one member of an IRB that reviews the research shall be a prisoner or a prisoner representative with appropriate background and experience to serve in that capacity. When the convened IRB reviews research involving prisoners (including initial review, continuing review, review of protocol modifications, and review of unanticipated problems involving risks to subjects or others), the prisoner or prisoner representative must be present as a voting member.

OHRP finds that NU IRB Panel B failed to meet this requirement when reviewing research protocol #0332-006, which involved prisoners.

(6) OHRP finds that NU does not have written IRB procedures that adequately describe the procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, the department or agency head, and OHRP of (i) any unanticipated problems involving risks to subjects or others; (ii) any serious or continuing noncompliance with 45 CFR part 46 or the requirements or determinations of the IRB; and (iii) any suspension or termination of IRB approval, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

OHRP also has the following concerns:

(7) [Redacted]

(8) [Redacted]

(9) [Redacted]

(10) [Redacted]

(11) [Redacted]

(12) [Redacted]

(13) [Redacted]

(14) [Redacted]

Action Required: By August 12, 2005, NU must submit to OHRP a satisfactory corrective action plan which addresses the findings and concerns stated above. For items (2) and (3) above, your corrective action plan should include IRB re-review of all active research protocols involving children, pregnant women, fetuses, and neonates. Please provide OHRP with a list of all such protocols.

At this time, OHRP would like to offer the following guidance:

(15) If the NU IRBs approve research contingent upon subsequent modifications or clarifications without requiring additional IRB review, OHRP recommends the following guideline: When the convened IRB requests substantive clarifications or modifications regarding the protocol or informed consent documents that are directly relevant to the determinations required by the IRB under HHS regulations at 45 CFR 46.111, IRB approval of the proposed research should be **deferred**, pending subsequent review by the convened IRB of responsive material.

(16) OHRP recommends that documentation for initial and continuing reviews conducted under an expedited review procedure include (a) the specific permissible categories (see http://www.hhs.gov/ohrp/humansubjects/guidance/expedited98.htm) justifying the expedited review and (b) documentation of the review and action taken by the IRB chairperson or designated reviewer and any findings required under the HHS regulations.

(17) The following criteria (see 48 FR 9266-9270) must be satisfied to invoke the exemption for research and demonstration projects examining "public benefit or service programs," as specified under HHS regulations at 45 CFR 46.101(b)(5): (a) The program under study must deliver a public benefit (e.g., financial or medical benefits as provided under the Social Security Act) or service (e.g., social, supportive, or nutritional services as provided under the Older Americans Act); (b) the research or demonstration project must be conducted pursuant to specific federal statutory authority; (c) there must be no statutory requirement that the project be reviewed by an IRB; and (d) the project must not involve significant physical invasions or intrusions upon the privacy of participants (see http://www.hhs.gov/ohrp/humansubjects/guidance/exmpt-pb.htm). This exemption is for projects conducted by or subject to approval of federal agencies, and is most appropriately invoked with authorization or concurrence by the funding agency.

(18) HHS regulations at 45 CFR 46.107(e) stipulate that no IRB member may participate in the initial or continuing review of any project in which the member has a conflicting interest. OHRP notes that NU's Vice President for Research serves as a voting member of the IRB. OHRP recommends that NU carefully assess whether the duties of this individual create any real or apparent conflicting interest with his role as an IRB member. If NU determines that he has any real conflicting interest, it would be appropriate for NU

to remove him from the NU IRB rosters.

(19) HHS regulations at 45 CFR 46.103(d) require that the adequacy of IRBs be evaluated in light of the anticipated scope of the institution's research activities, the types of subject populations likely to be involved, and the size and complexity of the institution. The regulations further require at 45 CFR 46.107(a) that IRBs be (a) sufficiently qualified through the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel; and (b) able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. Institutions have a profound responsibility to ensure that all IRBs designated under an OHRP-approved Assurance possess sufficient knowledge of the local research context to satisfy these requirements (see http://www.hhs.gov/ohrp/humansubjects/guidance/local.htm).

(20) 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 minutes of the IRB meeting, 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 minutes of the IRB meeting, 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.

(21) 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 on 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 all previous versions.

(22) The HHS regulations do not affect any applicable state or local laws or regulations which provide additional protections for human subjects [see 45 CFR 46.101(f)]. OHRP recommends that written IRB procedures describe applicable state and local laws and regulations relevant to the conduct of human subject research.

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,

Robert J. Meyer
Compliance Oversight Coordinator
Division of Compliance Oversight

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