DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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March 12, 2002

Dr. Michael M. Gottesman
Deputy Director for Intramural Research
National Institutes of Health
Building 1 – Room 114
1 Center Drive
Bethesda, MD 20892

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1000

Dear Dr. Gottesman:

As you know, the Office for Human Research Protections (OHRP) conducted an on-site not-for-cause evaluation of the human subject protection system at the National Institute on Alcohol Abuse and Alcoholism (NIAAA) on February 20 and 21, 2002. The evaluation involved meetings with senior institutional officials, the Chair and several members of the NIAAA Institutional Review Board (IRB), the IRB administrative staff, and intramural investigators who conduct research at the NIAAA. The evaluation included a review of the IRB records for all currently active intramural human subject research conducted by NIAAA, the minutes of NIAAA IRB meetings convened during the past year, and the written IRB policies and procedures.

OHRP Findings Regarding Systemic Protections for Human Subjects at NIAAA

Major Findings

Based on its evaluation, OHRP makes the following determinations regarding systemic protections for human subjects at NIAAA:

(1) OHRP finds that overall the NIAAA has implemented an outstanding system for protecting human research subjects involved in NIAAA-conducted intramural research. In particular, OHRP highly commends NIAAA for the following:

(a) Senior NIAAA and NIH officials displayed an on-going commitment to making the protection of human subjects one of the highest priorities of the institution.

(b) The NIAAA IRB's initial and continuing review of research, and its review of amendments to approved protocols, at convened meetings is both substantive and meaningful. Furthermore, the IRB records document that the NIAAA IRB routinely ensures that the criteria required for IRB approval under Department of Health and Humans Services (HHS) regulations at 45 CFR 46.111 are satisfied routinely for all research undergoing initial and continuing review.

(c) The minutes of the NIAAA IRB meetings meet and exceed the requirements of HHS regulations at 45 CFR 46.115(a)(2). In particular, the minutes of convened IRB meetings document (i) the IRB's findings with respect to the required criteria for IRB approval of research under HHS at 45 CFR 46.111, including protocol-specific information justifying the IRB's determination with respect to these criteria; and (ii) remarkably detailed discussions of controverted issues and their resolution.

(d) The NIAAA IRB appears to be sufficiently qualified through the experience and expertise of its members for the scope of research it reviews, in accordance with the requirements of HHS regulations at 45 CFR 46.107(a).

(e) The NIAAA IRB has sufficient staff, meeting space, and resources to support the IRB's review and recordkeeping duties, as required by HHS regulations at 45 CFR 46.103(b)(2).

(f) The NIAAA IRB Chair, members, and administrative staff displayed a sincere concern for the protection of human research subjects and appeared to be highly dedicated.

(g) The NIAAA investigators interviewed during the site visit demonstrated a culture of respect for the IRB process.

Additional Findings

(2) OHRP finds that the current IRB-approved informed consent documents for active NIAAA human subject research protocols were generally in compliance with the requirements of HHS regulations at 45 CFR 46.116, except for the following instances:

(a) The informed consent document for protocol #01-AA-0098 did not describe benefits to the subject that may reasonably be expected from the research, as required by HHS regulations at 45 CFR 46.116(a)(3).

(b) The informed consent document for protocol #99-AA-0113 lacked a clear and complete description of the research procedures for the third phase of the research, as required by 45 CFR 46.116(a)(1).

(3) OHRP is concerned that the NIAAA IRB failed to distinguish the separate HHS regulatory requirements for waiver or alteration of some or all of the required elements of informed consent, as set forth under HHS regulations at 45 CFR 46.116(d), and waiver of the requirement for the investigators to obtain a signed consent form for some or all subjects, as set forth under HHS regulations at 45 CFR 46.117(c), when it reviewed and approved two protocols where the purpose of the research was not fully disclosed to the subjects. Furthermore, OHRP is concerned that the NIAAA IRB failed to recognize in one instance that a waiver under either 45 CFR 46.116(d) or 46.117(c)(2) is not permissible unless the research involves no more than minimal risk to the subjects.

(4) OHRP finds that the NIAAA IRB records generally are complete and well-organized. However, OHRP finds that on occasion, the IRB records failed to include copies of correspondence between the IRB and investigators, as required by HHS regulations at 45 CFR 46.115(a)(4).

(5) 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 and not less than once per year. HHS regulations at 45 CFR 46.108(b) stipulate that except when an expedited review procedure is used, the IRB shall review research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. 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 more 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 finds that the NIAAA IRB did not consistently conduct continuing review of previously approved protocols within a period of one year or less from the date of the most recent prior IRB review. OHRP further finds that the NIAAA IRB's operating procedures for determining the time frame for continuing review do not ensure that such review occurs within a period of one year or less from the prior review date.

(6) OHRP finds that the institution does not have written IRB policies and procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5):

(a) The procedure for determining which projects require verification from sources

other than investigators that no material changes have occurred since previous IRB review.

(b) The procedure for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes are not initiated without prior IRB review unless necessary to eliminate apparent immediate hazards to subjects.

(c) The procedure for ensuring prompt reporting to OHRP of (a) any unanticipated problems involving risks to subjects or others; (b) any serious or continuing noncompliance with HHS regulations at 45 CFR Part 46 or the requirements or determinations of the IRB; and (c) any suspension or termination of IRB approval.

Required and Recommended Actions

Action 1 - Required: By April 11, 2002, please provide OHRP with a satisfactory corrective action plan to address the findings and concerns in items (2)-(7) above. Please include in your response a copy of any revised sections of the written NIAAA IRB policies and procedures.

Action 2 - Recommended: OHRP recommends that the NIAAA written IRB policies and procedures be revised to include a list of the documents that are provided to all IRB members for protocols undergoing initial and continuing review.

Action 3 - Recommended: OHRP recommends that the NIAAA IRB develop, and implement the use of, a standard approval letter to principal investigators for protocols approved by the IRB at the time of initial or continuing review, and that such approval letters include the date of expiration of IRB approval.

Action 4 - Recommended: OHRP recommends that NIAAA consider using a larger font size for the text in all informed consent documents.

Action 5 - Recommended: OHRP recommends that the first bullet under section 2.d of the Office of Human Subjects Research Information Sheet #6, Guidelines for Writing Informed Consent Document, be revised so that it is not limited to research involving subjects who are or may become pregnant.

OHRP appreciates the commitment of the NIAAA to the protection of human subjects, and is available to assist the NIAAA in developing any necessary corrective actions.

Sincerely,

Carol J. Weil, J.D.

Division of Compliance Oversight
Compliance Oversight Coordinator

cc: Dr. Alan L. Sandler, OHSR/NIH
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