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August 22, 2001

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

Dear Dr. Gottesman:

RE: OHRP Investigation Of Human Subject Protections Under Multiple Project Assurance (MPA) M-1000

Dear Dr. Gottesman:

The Office for Human Research Protections (OHRP) has reviewed your February 11, 2000 report which was submitted in response to OHRP's January 22, 2000 letter, regarding an audit of the National Cancer Institute (NCI) by the Food and Drug Administration (FDA). With the exception of NCI's Policy on Human Subjects, which requires updating as set forth in paragraph (5) below, NCI has satisfactorily addressed OHRP's concerns. As a result, OHRP is closing its investigation of NCI with the following findings:

(1) Based upon the FDA finding that the NCI IRB members were not familiar with 21 CFR 50 and 56, OHRP expressed concern that the NCI IRB might not be familiar with the parallel Department of Health and Human Services (HHS) regulations for the protection of human subjects research, 45 CFR Part 46. OHRP acknowledges NCI's statement that that all IRB members were familiar with the HHS regulations, the Belmont Report, and NIH's multiple project assurance.

(2) The FDA found that NCI's procedure for downloading informed consent documents already approved by the IRB allowed for spell checking and other minor changes to occur in the documents subsequent to their approval by the IRB. OHRP raised the concern that under this procedure, the IRB was not necessarily reviewing all finalized informed consent documents to ensure that the informed consent requirements of 45 CFR 46.116 were met, as required by HHS regulations at 45 CFR 46.109. OHRP acknowledges that NCI has altered its

review procedures to ensure that any spelling, font or punctuation changes to informed consent documents after IRB approval are made under the supervision of the IRB Chair. OHRP emphasizes that such expedited review by the Chair is only appropriate for minor changes to previously approved research under 45 CFR 46.109(b)(2).

(3) The FDA found that IRB members were not advised as to which protocols have undergone expedited review. Based upon our review of IRB minutes, OHRP finds that IRB members are provided at convened meetings with a list of expedited amendments approved the previous month. NCI clarified that the list of Expedited Amendments would include any new protocols approved by expedited review in accordance with 45 CFR 46.110, although it is rare that new protocols reviewed by the NCI IRB would meet the regulatory requirements for expedited review.

(4) The FDA found that IRB meeting minutes did not document the abstention of IRB members from voting on protocols in which they were involved as investigators. NCI acknowledged that its documentation of abstentions was inadequate, but stated that any member with a conflict of interest in a study did abstain from deliberation and voting on that study. NCI further stated that it was amending its documentation procedures to ensure accurate recording of abstentions due to conflicts of interest. Based upon its review of IRB minutes postdating NCI's change in documentation procedures, OHRP finds that the NCI IRB did record voting abstentions based upon conflict of interest.

(5) Based on the FDA's findings, OHRP expressed concern that the NCI IRB did not have the written policies and procedures required under 45 CFR 46.103(b)(4), including policies for conducting initial review, for determining which projects require review more often than annually, and for ensuring appropriate IRB review of amendments. NCI has informed OHRP that it is updating its Policy on the Protection of Human Subjects, currently in draft form, to ensure compliance with these requirements. OHRP finds that NCI's current draft Policy lacks procedures required under 45 CFR 46.103(b)(4) for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes are not initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to a research subject. OHRP further finds that NCI's current draft Policy does not contain written procedures, as required by 45 CFR 46.103(b)(5), for reporting unanticipated problems involving risks to subjects or others, or any serious or continuing noncompliance with the HHS human subject regulations or the determinations of the IRB, and any suspension or termination of IRB approval. OHRP expects the NCI IRB policies and procedures to be amended accordingly.

At this time, OHRP provides the following additional guidance to NCI:

(6) OHRP strongly recommends that IRB members absent themselves from the meeting room when the IRB votes on research in which they have a conflicting interest. Should the quorum fail during an IRB meeting because those with conflicts have excused themselves from the room, OHRP emphasizes that no actions can be voted upon unless the quorum is restored.

(7) In conducting the initial review of proposed research, IRBs must obtain information in sufficient detail to make the determinations required under HHS regulations at 45 CFR 46.111. Materials should include the full protocol, a proposed informed consent document, any relevant grant applications, the investigator's brochure (if one exists), and any advertising intended to be seen or heard by potential subjects. If the IRB uses a primary reviewer system, the primary reviewers should receive these materials sufficiently in advance of the meeting date to allow for in-depth prior review. All other IRB members should receive and review in advance of the meeting a protocol summary (of sufficient detail to make the determinations required under HHS regulations at 45 CFR 46.111), the proposed informed consent document, and any advertising material, but the complete documentation should be available to all members upon request. OHRP notes NCI's statement (Dr. Wyndham Wilson's February 8, 2000 letter to Ms. Carol Weil) that investigator drug brochures are available for review by the IRB at convened meetings, and recommends amendment of this policy in accordance with OHRP guidance.

(8) Continuing IRB review of research should be substantive and meaningful. In conducting continuing review of research not eligible for expedited review, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research, including (a) the number of subjects accrued; (b) a description of any adverse events or unanticipated problems involving risks to subjects or others and of any withdrawal of subjects from the research or complaints about the research; (c) a summary of any recent literature, findings obtained thus far, amendments or modifications to the research since the last review, reports on multi-center trials and any other relevant information, especially information about risks associated with the research; and (d) a copy of the current informed consent document. Primary reviewer systems may be employed, so long as the full IRB receives the above information. Primary reviewers should also receive a copy of the complete protocol including any modifications previously approved by the IRB (see OPRR Reports 95-01). Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

(9) The draft Policy at page 3 discusses IRB membership requirements under the HHS regulations protecting human subjects, and misstates the HHS regulation number as 45 CFR 46.106. The correct regulatory citation is 45 CFR 46.107.

(10) The draft Policy states that expedited review procedures may be used to review and approve minor changes in previously approved research, in accordance with HHS regulations at 45 CFR 46.110(b)(2). OHRP recommends that institutions conducting human subject research adopt policies describing the types of minor changes in previously approved research which can be approved by expedited review in accordance with these regulations.

OHRP appreciates NCI's continued commitment to the protection of human research subjects. Feel free to contact me if you have any questions.

Sincerely

Carol J. Weil, J.D.
Compliance Oversight Coordinator
Division of Human Subject Protections

cc: Dr. Michael A. Carome, OHRP
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