DEPARTMENT OF HEALTH & HUMAN SERVICES

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January 24, 2001

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

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

Research Projects:	**Mechanisms of Drug Disposition in Hair**
Intramural Institute:	**National Institute on Drug Abuse (NIDA)**
Principal Investigator:	**Dr. Edward J. Cone**

Dear Dr. Gottesman:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed your report dated July 12, 1999 regarding possible noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR Part 46) involving the above referenced research. OHRP apologizes for the delay in responding to your report.

Based upon its review of your written report, OHRP makes the following determinations regarding the above referenced research:

(1) OHRP finds that NIDA has adequately addressed the issues surrounding participation of subjects who are attempting to remain abstinent from drugs of abuse, as well as risks from reporting of remuneration to government or private entities which might have an interest in the subjects earnings. In specific, OHRP notes that your report stated the following:

(a) "[the] protocol itself requires that subjects "be experienced, current users of opioids and stimulants ..., have abused opioids and stimulants for more than two years, have used cocaine at least three times during 1 month immediately prior to admission ..., and produce at least one urine toxicology test positive for cocaine."

(b) "A subject expressing interest in drug abuse treatment at this time is offered a referral to treatment which, if accepted, would make him ineligible to participate in this study."

(c) "As part of the recruiting/screening process, all subjects at the NIDA [Intramural Research Program (IRP)] receive, and are asked to sign, a disclosure statement regarding 'Research earnings as reportable income to the Internal Revenue Service (IRS)' This statement informs subjects that research 'compensation' (remuneration) is reportable income to the IRS, that it is their responsibility to report an such payments, and that NIDA does not report to the IRS because of confidentiality considerations."

(2) HHS regulations at 45 CFR 46.116(b)(4) require that, when appropriate, informed consent include a description of the consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject. Your report stated the following:

(a) "The informed consent document does not mention as a risk the chance that subjects' exposure to drugs during the research will be detected after they leave the study."

(b) "Subjects who insist on leaving immediately ("against medical advice") are advised by the staff of the risk of doing so."

The consequences of withdrawal from the study against medical advice are provided to the subject only at the time of withdrawal. OHRP finds that it would have been appropriate for such consequences to be described in the informed consent documents, in accordance with HHS regulations at 45 CFR 46.116(b)(4).

Required Action - NIDA must submit to OHRP a corrective action plan to ensure that subjects enrolled in the above referenced research (as well as all future subjects) are informed of the consequences of their withdrawal from the study against medical advice.

OHRP has the following additional questions and guidance:

(1) HHS regulations at 45 CFR 46.116(a)(8) require that informed consent include a statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is

otherwise entitled. Furthermore, HHS regulations at 45 CFR 46.116 stipulate that an investigator shall seek consent only under circumstances that provide the prospective subject sufficient opportunity to participate and that minimize the possibility of coercion or undue influence.

OHRP is concerned that statements made in the informed consent document and the NIDA Participant Compensation document regarding the fifty percent loss of payment for leaving the study without medical approval failed to minimize the possibility of coercion or undue influence as required by HHS regulations at 45 CFR 46.116. Additionally, OHRP is concerned that the these statements fail to satisfy the requirements of HHS regulations at 45 CFR 46.116(a)(8) relating to voluntary withdrawal at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Please respond.

(2) OHRP acknowledges NIDA's efforts in utilizing a central recruiting unit to obtain equitable recruitment of all population groups in general. Your report states that "[recruiting] efforts from time to time include local college campuses, as well as other community sites." OHRP is concerned that, due to the extended inpatient stay for the above referenced research, recruitment of subjects from a diverse range of applicants which does not place an undue burden on any one particular segment of society (e.g., low income drug abusers) may be difficult. Please respond. With your response please provide an indication of what efforts were made to recruit subjects from a wide population for this particular study (as well as any Institutional Review Board (IRB) approved recruitment material) and what efforts, if any, were made to seek subjects of diverse socioeconomic status and diverse geographic areas.

(3) OHRP notes that approval for the above referenced research was granted on January 10, 1995 but this approval was contingent on a change in NIDA DIR policy on the subcutaneous administration of cocaine. In particular, OHRP notes the following:

(a) The minutes of the January 10, 1995 IRB meeting stated:

(i) "The Acting Clinical Directors are planning a meeting in the near future, including NIDA DIR and outside experts, to review the policy on subcutaneous dose limits."

(ii) "The protocol would not begin unless the suggested change in the policy is approved by the Institute."

(b) The minutes of the February 13, 1996 IRB meeting stated:

"[this] study was approved for implementation in October 1995, and the first subject was recruited in November 1995."

In reviewing the documents provided with your report, no information is provided indicating that a change in NIDA policy regarding subcutaneous administration of cocaine had been approved. Please respond. In your response please indicate if the NIDA policy on subcutaneous administration of cocaine has been changed, what the current policy is, and by what mechanism the IRB and investigator were made aware of such a change in policy.

(4) In reviewing IRB files submitted with your report, OHRP notes that the IRB appears to approve research contingent upon substantive modifications or clarifications without requiring additional review by the convened IRB. OHRP recommends the following guidelines in such cases: (i) When the convened IRB requests substantive clarifications, protocol modifications, or informed consent document revisions, IRB approval of the proposed research must be deferred, pending subsequent review by the convened IRB of responsive material. (ii) Only when the convened IRB stipulates specific revisions requiring simple concurrence by the investigator may the IRB Chair or another IRB member designated by the Chair subsequently approve the revised research protocol on behalf of the IRB under an expedited review procedure.

(5) 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. Unless a primary reviewer system is used, all members should receive a copy of the complete documentation. These materials should be received by members sufficiently in advance of the meeting date to allow review of this material.

(6) HHS regulations at 45 CFR 46.115(a)(2) require that the minutes of IRB meetings document the vote on all IRB actions including the number of members voting for, against, and abstaining. In order to document the continued existence of a quorum, OHRP strongly recommends that votes be recorded in the minutes using the following format: Total = 15; Vote: For-14, Opposed-0, Abstained-1 (NAME).

(7) OHRP recommends that IRBs affix the approval and expiration dates to all approved informed consent documents and stipulate that copies of these dated documents must be used in obtaining consent. This procedure helps ensure that only the current, IRB-approved informed consent documents are presented to subjects and serves as a reminder to the investigators of the need for continuing review.

The approval date should be the most recent of the following: (a) date the protocol and informed consent document were initially reviewed and approved by the IRB; (b) date of the most recent IRB continuing review and approval of the protocol and informed consent document; or (c) date that the IRB approved the most recent modification to the informed

consent document. In all three circumstances, the approval date which appears on the consent document is the date of approval of the most recent version of the consent document. The expiration date should correspond to the end of the current IRB approval period.

Please provide to OHRP a response to the required action and the above questions and concerns no later than March 16, 2001

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. Ruth Kirschstein, Acting Director, NIH
Dr. Alan I. Leshner, NIDA
Dr. David Gorelick, IRB Chairperson, NIDA
Dr. Alan L. Sandler, OHSR, NIH
Commissioner, FDA
Dr. David Lepay, FDA
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Dr. Greg Koski, OHRP
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