DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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December 12, 2000

Michael Gottesman, M.D.
Deputy Director for Intramural Research
Building 1, Room 114
9000 Rockville Pike
National Institutes of Health
Bethesda, MD 20892

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

Research Project: Allelic Variation in Schizophrenia
Project number: 96-M-0110
Principal Investigator: Anil K. Malhotra, M.D.

Research Project: Study of CNS Parameters in Normal Controls to be Compared with Age-Matched Schizophrenic, Depressed, and Personality Disordered Patient Populations
Project number: 83-M-0114
Principal Investigator: David Pickar, M.D.

Research Project: The Behavioral, Neuroendocrine and Neuropsychological Effects of Ketamine in Schizophrenic Patients and Healthy Volunteers
Project number: 93-M-0175
Principal Investigator: David Pickar, M.D.

Research Project: I-123 (RR, RS, SS or SR) 3-Quinuclidynl 4-Iodobenzilate (I-123 QNB) Distribution and Function in Neuropsychiatric Patients and Normal Volunteers
Project number: 90-M-0007
Principal Investigator: Daniel R. Weinberger, M.D.

Research Project: and I-123 IBZM SPECT Studies of D2 Receptor Distribution and Function in Neuropsychiatric Patients and Normal Volunteers

Project number: 92-M-0024
Principal Investigator: Daniel Weinberger, M.D.

Dear Dr. Gottesman:

The Office for Human Research Protections (OHRP) has reviewed your report of November 17, 2000 regarding the above referenced research projects.

OHRP has conducted a complete review of the documents provided with your report, which includes information regarding psychiatric research protocols in which the subject C.P. was involved.

Based upon its review of your October 26, 1998 and November 17, 2000 reports, OHRP makes the following determinations:

A. OHRP Findings Regarding the Initial Complaint from the Parents of C.P.

(1) OHRP finds that human subject research involving the manipulation of antipsychotic agents for research purposes was conducted on C.P., as well as on other subjects, by investigators at the National Institute of Mental Health (NIMH) without Institutional Review Board (IRB) review and approval and without the legally effective informed consent of the subjects, in contravention of the requirements of HHS regulations at 45 CFR 46.109(a) and 45 CFR 46.116, respectively. In specific, C.P. and three other NIMH research subjects were placed on fixed doses of olanzapine (at 5 mg and/or 20 mg per day) for research purposes prior to undergoing research SPECT studies without IRB review and approval or the legally effective informed consent of the subjects.

Corrective Actions: OHRP acknowledges the IRB's intention to recontact the subjects enrolled in the SPECT imaging protocols who did not give informed consent for intervention with fixed doses of olanzapine for research purposes. OHRP looks forward to receiving the NIMH IRB's plan for contacting subjects involved in these research activities that were conducted without appropriate IRB approval or informed consent and informing them of these events.

Furthermore, OHRP acknowledges that NIMH has (i) implemented over the past three years a variety of educational programs to ensure that all investigators understand the requirements of the HHS regulations for protection of human subjects; and (ii) admonished the investigators responsible for the above cited deficiencies. OHRP has determined that these corrective actions are appropriate under the NIH Multiple Project Assurance (MPA).

B. OHRP Findings Regarding Project #96-M-0110

(2) OHRP finds that the informed consent documents reviewed and approved by the IRB for this research project prior to August 28, 1998 failed to include a complete description

of the procedures to be followed, and identification of any procedures which are experimental, as required by HHS regulations at 45 CFR 46.116 (a)(1). In specific, OHRP notes that the informed consent document stated that venous blood samples will be used to extract DNA, but there was no description of the plan to use the subject's blood to establish cell lines prior to August 28, 1998.

Corrective Action: OHRP acknowledges that (i) this deficiency was corrected at the time of the IRB's continuing review of this protocol on August 28, 1998; and (ii) the NIMH IRB has implemented a policy to ensure that research procedures involving the establishment of cell lines from research subjects' biologic samples will be described in informed consent documents. OHRP has determined that these corrective actions are appropriate under the NIH MPA. Furthermore, OHRP acknowledges that the research has been terminated.

C. OHRP Findings Regarding Project #93-M-0175

(3) OHRP finds that the informed consent documents reviewed and approved by the IRB for this research project failed to include an adequate description of the reasonably foreseeable risks and discomforts, as required by HHS regulations at 45 CFR 46.116(a)(2). In specific, OHRP finds that after 1995, it would have been appropriate for the informed consent document to more clearly state that the dose of ketamine to be administered to the subjects could cause delusions, hallucinations, and thought disorder acutely and that some psychotic symptoms could occur hours or days later. Furthermore, OHRP acknowledges that the IRB was not made aware of relevant published data regarding the safety of ketamine challenge studies when it conducted its continuing review of this research project in 1996 and 1997.

Corrective Action: On October 24, 2000, the NIMH IRB suggested that "....investigators be reminded that their continuing reviews be updated with any relevant literature and that consent forms be updated in a parallel fashion." Please clarify whether this suggestion was or will be implemented. If so, please describe NIMH's procedures for implementing this plan.

(4) OHRP finds that NIMH failed to promptly report to appropriate NIH officials and OPRR, in accordance with HHS regulations at 45 CFR 46.103(b)(5), an unanticipated problem involving risk to a subject where an error made by the Clinical Center pharmacy resulted in a ten-fold higher dose of ketamine being administered to a subject.

Corrective Action: OHRP acknowledges that interim guidelines for reporting adverse events to NIH IRBs, clinical directors, the Clinical Center Director, FDA, OBA, OHSR

and OHRP has been circulated to all NIH clinical investigators, and at IRB meetings. OHRP has determined that these corrective actions are appropriate under the NIH MPA.

(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. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval. OHRP finds that extensions of approval beyond the expiration date were granted for protocol 93-M-0175, as well as protocol 90-M-0007, by the NIMH IRB.

Corrective Action: OHRP acknowledges that NIMH now strictly forbids subject accrual beyond the expiration date of IRB approval. OHRP has determined that this corrective action is appropriate under the NIH MPA.

D. OHRP Findings Regarding NIMH's Systemic Protections for Human Subjects

(6) HHS regulations at 45 CFR 46.111(b) require that the IRB ensure that additional safeguards have been included in research to protect the rights and welfare of vulnerable subjects. OHRP finds that the IRB records provided with your initial report of October 26, 1998 failed to demonstrate that the IRB consistently considered such safeguards for research protocols that involved subjects who were likely to be vulnerable to coercion or undue influence because of impaired capacity to consent.

Corrective Action: OHRP acknowledges that NIMH has created a system to provide independent capacity assessment of subjects with psychiatric illnesses that could affect capacity to provide informed consent, procedures for independent evaluation for subject suitability, and procedures for monitoring the progress of subjects in protocols to identify any instances where decisional capacity of subjects may need to be reassessed. OHRP has determined that these corrective actions are appropriate under the NIH MPA.

(7) Based on NIMH's response to OHRP's concern regarding the adequate continuing review procedures utilized by the NIMH IRB prior to 1998, OHRP finds that the current NIMH IRB procedures for continuing review appear to be adequate.

(8) HHS regulations at 45 CFR 46.116 require that the information provided in informed consent documents be in language understandable to the subjects. OHRP finds that many of the IRB-approved informed consent documents submitted with your initial report appear to include complex language (including complex sentence structure and vocabulary) that would not be understandable to all subjects.

Corrective Action: OHRP acknowledges that the NIMH IRB has added a lay patient advocate to its membership to help identify language in consent documents that is complex or potentially confusing. OHRP has determined that this corrective action is appropriate under the NIH MPA.

E. OHRP Concerns and Question Regarding the Initial Complaint from the Parents of C.P.

(9) In his November 14, 2000 memorandum to you, Dr. Robert Desimone stated that "[i]t cannot be ruled out that the medication regimen introduced during C.P.'s hospitalization could have contributed to his subsequent deterioration." Given that C.P.'s family was denied financial assistance for hospitalization due to his deterioration after discharge from NIMH research, has he or his family been informed of this reassessment, and that they may pursue reimbursement by a claim made under the Federal Tort Claims Act? Furthermore, would it be appropriate for all NIH informed consent documents to describe this remedy for seeking financial compensation in the event a subject is injured because of alleged negligence or wrongful acts or omissions of NIH researchers who are Federal employees acting within the scope of their employment?

F. OHRP Concerns Regarding Project #97-M-0159

(10) OHRP is concerned that the informed consent documents reviewed and approved by the IRB for this project failed to include an adequate description of the reasonably foreseeable risks and discomforts as required by 45 CFR Section 46.116(a)(2) (i.e., several fairly common side effects of olanzapine, such as swelling, increased appetite, dizziness, prolactin increase, as well as rare side effects such as slow heart rate, rash, neuroleptic malignant syndrome, seizures, leukopenia, priapism, were not listed in the informed consent document.) Please respond.

G. OHRP Concerns Regarding #89-M-0160

(12) The minutes of the October 10, 2000, IRB meeting indicated that the IRB expressed concern regarding "...the appropriateness of keeping the patient at the NIH for more than a month while optimizing his treatment...." They suggested that the principal investigator consider writing a "treatment optimization protocol." Please clarify whether this suggestion by the IRB has been or will be implemented.

Please submit to OHRP your response to the above questions and concerns no later than January 15, 2001.

OHRP appreciates your institution's continued commitment to the protection of human research subjects. Do not hesitate to contact me if you have any questions regarding this matter.

Sincerely,

Kristina C. Borror, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Ruth Kirschstein, Acting Director, NIH

Dr. Alan Sandler, Director, OHSR, NIH
Dr. Steven E. Hyman, Director, NIMH
Dr. Donald Rosenstein Chair, IRB, NIMH
Dr. Daniel R. Weinberger, NIMH
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael A. Carome, OHRP
Dr. J. Thomas Puglisi, OHRP
Dr. Katherine Duncan, OHRP
Mr. George Gasparis, OHRP
Dr. Jeffrey M. Cohen, OHRP
Dr. Clifford C. Scharke, OHRP
Mr. Barry Bowman, OHRP