DEPARTMENT OF HEALTH & HUMAN SERVICES

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January 22, 2001

Michael Gottesman, M.D.
Deputy Director for Intramural Research
National Institutes of Health
Building 1, Room 114
Bethesda, MD 20982

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

Project: The Evaluation and Follow-up of Patients with Bipolar Disorder
Principal Investigator: Kirk D. Denicoff, M.D.
Protocol number: 97-M-0039

Dear Dr. Gottesman:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed the November 10, 1999 report submitted by your institution regarding the above referenced research project conducted at the National Institutes of Mental Health (NIMH). OHRP apologizes for the delay in responding to your report.

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

(1) The complainant alleged that the IRB failed to ensure appropriately documented informed consent, as required by HHS regulations at 45 CFR 46.111(a)(5), and failed to make the required findings for waiving the requirement for documentation of informed consent, as required by 45 CFR 46.116(d).

OHRP acknowledges that in his November 9, 1999 memorandum to Dr. Michael Gottesman, Dr. Robert Desimone stated that (i) the series of patients reported in the journal article entitled "Olanzapine in treatment-resistant bipolar disorder"(*Journal of Affective Disorders* (1998) 49: 119-122) received olanzapine as clinically indicated; (ii)

these patients provided written informed consent that medications would be given as clinically indicated; and (iii) research data reported in the journal article was obtained under a formal, Institutional Review Board (IRB)-approved protocol, protocol number 97-M-0039, and with the written informed consent of each subject. OHRP finds that the above-mentioned research was in compliance with HHS regulations at 45 CFR 46.111(a)(5).

(2) HHS regulations at 45 CFR 46.111(b) require that, in order to approve research, the IRB must determine that additional safeguards have been included in research to protect the rights and welfare of vulnerable subjects. It appears that some subjects were likely to be vulnerable because of active mania and subsequent cognitive impairment. The preprint of the article "The Stanley Foundation Bipolar Treatment Outcome Network: II. Demographics and Illness Characteristics of the First 261 Patients" (*Journal of Affective Disorders*, in press) stated that "[a]t study entry...18% showed ultradian [more than one episode per day in four or more days per week] or continuous cycling." OHRP is concerned that (i) subjects in such states may not be capable of giving informed consent or are likely to be vulnerable to coercion or undue influence; and (ii) there appears to be little indication that any additional protections were considered for such potentially vulnerable subjects.

Corrective Action: OHRP acknowledges that NIMH has moved to "develop an independent capacity assessment team and to provide independent consent monitoring as part of our new clinical core evaluation team." This should adequately address these concerns in the future.

As a result, there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

At this time, OHRP provides the following additional recommendations and guidance regarding the above-referenced research:

(3) The original IRB-approved protocol, as well as a subsequent IRB-approved protocol amendment, referenced several psychiatric rating scale instruments and a "Daily Life Chart Method" that was to be filled out daily by the subject. OHRP notes that the information contained in these documents appears to be pertinent to IRB determinations required by HHS regulations at 45 CFR 46.111. I would be appropriate for the IRB to review all such instruments prior to approval of research.

(4) OHRP is concerned that the informed consent document approved by the IRB for this study appeared to include complex language that would not be understandable to all subjects. OHRP emphasizes that the information provided in the informed consent documents must be in language understandable to all subjects, as required by HHS regulations at 45 CFR 46.116.

(5) OHRP recommends that the informed consent documents be assessed to ensure inclusion of the following elements required by HHS regulations at 45 CFR 46.116 (a):

(a) Section 46.116(a)(1): the expected duration of the subject's participation; and a complete description of the procedures to be followed, and identification of any procedures which are experimental. In specific, OHRP notes the following:

(i) Individuals undergoing a lumbar puncture were expected to follow a diet low in monoamines, which was not mentioned in the consent form, although was present in an attachment. It is not clear if this attachment was part of the informed consent document.

(ii) The "daily life chart method" was not fully explained in the informed consent document; subjects were expected to fill out a questionnaire daily for the duration of the study regarding their mood and functional impairment which could have been considered onerous by some subjects.

(iii) The preprint of the article "The Stanley Foundation Bipolar Treatment Outcome Network: I. Longitudinal Methodology" (*Journal of Affective Disorders*, in press) stated that "[w]e also wish to elucidate...possible genetic correlates of treatment response in Network patients...." Genetic testing was not mentioned in the informed consent document.

(b) 45 CFR 46.116(a)(2): an adequate description of the reasonably foreseeable risks and discomforts. In specific, it may have been appropriate for informed consent document to indicate that questions asked during the study may be upsetting to the subjects.

(c) Section 46.116(a)(3): An adequate description of any benefits to the subject or others that may *reasonably* be expected from the research.

(d) Section 46.116(a)(4): A description of appropriate alternative procedures or courses of treatment that might be advantageous to the subject.

(6) OHRP notes that there was some confusion regarding the age range of subjects. The initial application was marked "18-65 yrs" on the face page, "18-99" on the Clinical Screening Protocol, and "at least 18 years old" in the Study Procedure. The continuing review application dated October 8, 1997 noted one of these discrepancies and stated that the current, correct age should be "at least 18 years old"; however, the face page on the continuing review application dated 10/6/98 was marked "18-65 yrs." OHRP recommends that the IRB ensure that all such information be consistently presented.

OHRP appreciates your institutions' 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. Alan Sandler, OHSR, NIH
Dr. Trey Sunderland, Chair, NIMH IRB
Dr. Kirk Denicoff, NIMH
Dr. Robert M. Post, NIMH
Dr. Robert Desimone, NIMH
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