DEPARTMENT OF HEALTH & HUMAN SERVICES

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RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1138

Research Project: Predictors of Course and Outcome in Acute Mania: A Prospective, Naturalistic Follow-up Study
Principal Investigator: Susan McElroy, MD
UC Study Number: 92-4-14-2

Dear Dr. Harrison, Mr. Cohen, Mr. Pishioneri and Dr. Warden:

The Office for Human Research Protections (OHRP) has reviewed the March 27, 2001 report submitted by your institutions regarding the above referenced research project conducted at the University of Cincinnati (UC).

Based upon its review, OHRP makes the following determinations.

(1) The journal article entitled "Olanzapine in treatment-resistant bipolar disorder"(*Journal of Affective Disorders* (1998) 49: 119-122) stated that "[r]esponse to olanzapine was rated with the Clinical Global Impression Scale (Guy, 1976) modified for bipolar disorder (CGI-BP)." OHRP finds that use of this rating scale in subjects was not approved by the Institutional Review Board (IRB), in contravention of the requirements of Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(b)(4)(iii).

Corrective Actions: OHRP acknowledges that the investigator has been informed that any modifications to an IRB-approved research protocol such as having subjects complete additional rating scales must be submitted as an amendment to the protocol to be reviewed and approved by the IRB. OHRP also notes that the investigator has completely revised the protocol and informed consent document to address the issues outlined in OHRP's December 8, 2000 letter, as well as other concerns expressed by the UC IRB.

(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. OHRP acknowledges that a quiz was used by the investigators to ascertain whether subjects had some understanding of the informed consent. However, OHRP finds no indication that any other additional protections were considered by the IRB for such vulnerable subjects.

Corrective Actions: OHRP acknowledges that the revised protocol approved by the IRB includes additional protections for vulnerable subjects such as (i) excluding subjects who fail to receive a perfect score on the "informed consent comprehension tool" more than once; (ii) keeping the subject's non-research, primary psychiatric care provider informed of the subject's progress; (iii) allowing subjects as much time as needed to decide about participation and encouraging consultation with family members and others; and (iv) providing educational information to the subject and reviewing it with them to increase their appreciation of their role in the research.

(3) HHS regulations at 45 CFR 46.111(a)(1) and (2) require that, in order to approve research, the IRB determine that risks to the subjects are minimized and are reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge that may reasonably be expected to result. At initial review, one reviewer had

some questions/concerns regarding the indefinite nature of the length of the study and asked "how many subjects are required to determine predictive power in the statistics[?]" The principle investigator responded that "...biostatistical nuances...are not appropriate concerns of an IRB and will therefore not address these issues...." OHRP finds that the IRB was inappropriately rebuffed in its attempt to obtain information to make the determinations required for approval of research under section 45 CFR 46.111(a)(1) and (2).

Corrective Actions: OHRP acknowledges the IRB's understanding that issues related to scientific study design are well within the purview of the IRB. UC also noted that the investigator has been so informed and she and her staff have attended a mandatory education session focusing on compliance with OHRP regulations and the role of the IRB.

(4) OHRP finds that the informed consent documents reviewed and approved by the IRB for this research project 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, in a letter requesting approval of the addition of the daily "NIMH Life Chart" (and some rating scales) the principal investigator incorrectly stated "...the informed consent statement does not require modification to include these changes...." As a result, an appropriately revised informed consent document was not approved by the IRB when it approved the use of the "NIMH Life Chart."

Corrective Actions: OHRP acknowledges that the IRB has approved a revised informed consent document that includes this information.

(5) HHS regulations at 45 CFR 46.116(a)(2) require that informed consent documents include an adequate description of the reasonably foreseeable risks and discomforts to the subjects. OHRP finds that there was no statement in the IRB-approved informed consent document indicating that questions asked during the study may be upsetting to the subjects.

Corrective Actions: OHRP acknowledges that the IRB has approved a revised informed consent document that includes this information.

(6) The IRB-approved protocol indicated that the study could involve children as young as 12 years old. OHRP finds that there was no indication that the IRB ever discussed the inclusion of children. Where HHS regulations require specific findings on the part of the IRB, such as approving research involving children (see 45 CFR 46.404-407), the IRB should document such findings.

Corrective Actions: OHRP acknowledges that no children have been enrolled in the study by investigators at UC and that the revised protocol approved by the IRB does not

include children.

OHRP finds that the preceding corrective actions adequately address OHRP's findings and are appropriate under the UC Multiple Project Assurance. As a result of the above determinations, 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 offers the following additional guidance.

(7) HHS regulations at 45 CFR 46.116 require that the information provided in the informed consent documents be in language understandable to the subject. OHRP recommends that the IRB ensure that approved informed consent documents do not include complex language that would not be understandable to all subjects.

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: Mr. Michael Walton, Medical Center Director, Chillicothe VAMC
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