DEPARTMENT OF HEALTH & HUMAN SERVICES

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December 12, 2000

Dr. Alison F. Richard
Provost
Yale University
P.O. Box 208236
New Haven, CT 06520-8236

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1452

Research Project: Delaying or Preventing Psychosis: A Clinical Trial of Olanzapine in Persons Prodromal to Psychosis
Principal Investigator: Thomas H. McGlashan
Yale Protocol Number: HIC 9253
HHS Project Number: K05 MH01654

Dear Dr. Richard:

The Office for Human Research Protections (OHRP) has reviewed your report of October 2, 2000 regarding the above referenced research project.

OHRP has conducted a complete review of the documents provided with your report. Based upon its review, OHRP makes the following determinations regarding the above referenced research.

(1) HHS regulations at 45 CFR 46.404-407 require specific findings on the part of the IRB for approval of research involving children. OHRP's review of Institutional Review Board (IRB) documents for this research reveals no evidence that the IRB made the required findings when initially reviewing this research involving children.

(2) OHRP finds that Yale University (Yale) has already taken appropriate corrective actions to address Finding (1). In specific, OHRP acknowledges that the Yale IRB (i.e., HIC-I) performed a detailed continuing review of this protocol in September of this year,

at which time the findings required under 45 CFR 46.404-407 were made and documented. OHRP finds that the determination made by the Yale IRB are consistent with the HHS regulations.

(3) OHRP finds that documentation of informed consent for some subjects may not have satisfied the requirements of HHS regulations at 45 CFR 46.117(a). OHRP acknowledges your report that there was some confusion regarding informed consent documents that were misplaced or not signed.

Corrective Action: OHRP acknowledges that efforts were made to rectify these occurrences, and a letter to the study coordinator stated that "[t]he committee will consider the absence of this documentation in the future a serious breach of federal regulations and HIC policies, and suspend approval of the protocol." OHRP has determined that these corrective actions are appropriate under the Yale Multiple Project Assurance.

OHRP has the following additional concerns and questions regarding the above-referenced research project:

(4) 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 is concerned that the IRB records provided with your report failed to demonstrate that the IRB considered such safeguards for the subjects in this project, some of whom the investigators stated would develop psychoses in the course of the research. There appears to be no mention in the protocol, the informed consent document, or IRB discussions regarding how to ensure continuing informed consent of adult subjects who become psychotic during their participation in research and lose the capacity to consent. Please respond.

(5) OHRP is concerned that the informed consent documents reviewed and approved by the IRB for this research project may have 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, a letter of collaboration dated October 6, 1998 from Dr. Ralph E. Hoffman stated that his "...role in the project is to oversee the neuropsychological and neuroimaging aspects of the study." There is no mention in the protocol or the informed consent document of imaging in this project. Please clarify.

(6) It appears 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 notes the following:

(a) It appears that it would be appropriate for the informed consent and assent documents to describe the plan for parental notification of illicit drug use as an additional risk to the children.

(b) It appears that it would be appropriate for the description of priapism in the informed consent document (i.e., "problems in males that may cause the penis to stay erect too long") be expanded to indicate that this side effect usually occurs without sexual desire and is accompanied by pain.

(c) The IRB-approved protocol states that "[t]he side effects of the medications will be outlined as well as other possible risks of participating, eg., moments of emotional upset when discussing troubled feelings or life events." However, it appears that this risk of emotional upset was not described in any informed consent documents for this project.

(d) The informed consent document states "[w]hile the clinical goal is to help you feel better and in more control of you life, it is possible that you will feel worse. This is a risk of your clinical condition, not a risk of being in the study." This statement appear not to take into account "feeling worse" due to olanzapine side effects.

(e) Given that the efficacy of olanzapine in preventing progression of a prodromal state to schizophrenia has not been established and is being assessed by this research, OHRP is concerned that the following statement in the informed consent document may not be appropriate: "[i]f you are randomly assigned to receive placebo you will be at risk for receiving inactive treatment which could result in a worsening of your condition."

Please respond.

(7) OHRP is concerned that the IRB may have failed to receive and review the assessment interview instrument and the NIMH grant application "Early Detection and Intervention in Psychosis" (K05 MH01654-02), which includes a detailed plan for recruitment for this project, with proposed press releases. 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. Furthermore HHS regulations at 45 CFR 46.103(f) requires that the IRB review and approve all Federal grant applications. Please respond.

(8) HHS regulations at 45 CFR 46.111(a)(1) require that, in order to approve research, the IRB shall determine that risks to the subjects are minimized. The IRB sought advice from several experts in their "accelerated continuing review." Several experts suggested weight-based dosing for adolescents. The investigators did not follow this advice, stating that "of the 32 patients randomized so far, the mean...weight has been 147...pounds." However, subjects enrolled in the future could be considerably lighter, especially given

the plan to enroll subjects as young as 12 years of age, and it appears that weight-based dosing may be a prudent modification to minimize risks to subjects. Please respond.

(9) HHS regulations at 45 CFR 46.111(a)(7) require that research protocols have adequate provisions to protect the privacy of subjects and the confidentiality of data collected. OHRP notes that in a paper in *Connecticut Medicine* in June of 2000, Miller and McGlashan identified a subject by first name and life history (unlike another publication by this group, there is no indication that the case was disguised.) OHRP is concerned that this paper may result in a potential violation of privacy of the subject described. Please respond.

Please submit to OHRP your response to the above questions and concerns no later than January 29, 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: Mr. Allen Brown, CEO, The APT Foundation
Mr. James Jerrell, President, Community Consultation Board, Inc.
Dr. Selby C. Jacobs, Director, Connecticut Mental Health Center
Mr. Philip E. Rubin, Vice President, Haskins Laboratories
Mr. Lawrence E. Marks, Director, John B. Peirce Laboratory, Inc.
Ms. Sarah Cohn, Director Legal Affairs/Risk Management, Yale-New Haven Hospital
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