DEPARTMENT OF HEALTH & HUMAN SERVICES

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April 30, 2001

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

Research Project: Serial CSF Studies in Combat Veterans with PTSD
Principal Investigator: Thomas D. Geracioti, M.D.
UC Study Number: 93-6-3-3 and 98-7-31-1

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

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

Based upon its review, OHRP makes the following determinations:

(1) OHRP finds that when reviewing the above-reference protocol application, the Institutional Review Board (IRB) did not receive sufficient information to make the determinations required for approval of research under Department of Health and Human Services (HHS) regulations at 45 CFR 46.111. Furthermore, OHRP finds that changes were made to the protocol without IRB approval, in contravention of the requirements of HHS regulations at 45 CFR 46.103(b)(4)(iii). For example, OHRP finds the following:

(a) Publications resulting from this research described discontinuation of psychoactive medications about 2 weeks prior to lumbar puncture and prescription of a "controlled low-monoamine diet for at least 3 days before admission...." Neither of these was described in the IRB-approved protocol or informed consent document.

(b) On November 10, 1994, the principal investigator requested a change to the protocol to include enrollment of patients with post traumatic stress disorder (PTSD). The changes to the protocol were limited only to a change in the title and the change to the informed consent document was limited to the addition of a sentence asking about trauma history and a reference to PTSD. The IRB apparently did not see a new protocol.

(c) On May 28, 1996, the co-principal investigator requested approval of "some minor changes" to the informed consent document for the study. The changes included the addition of viewing a video tape "which may...remind [the subject] of past events and feelings." There was no mention that the tape was of a combat scene, intended to elicit PTSD symptoms. The IRB was not specifically alerted to this change and whether it may increase the risk of the protocol. Another change that the IRB was not specifically alerted to was the increase in compensation from $250 to $500. Given the substantial changes to the protocol since initial review, it appears that it would have been appropriate for the IRB to request a revised protocol.

(d) In October of 1997, the principal investigator requested approval of an advertisement, which listed the compensation for the research at $750. The IRB was never specifically alerted to this change in the protocol, which could have increased the possibility of undue influence.

Corrective Actions: OHRP notes that a recent education session presented to the IRB re-emphasized the importance of comparing the protocol to the informed consent document to ensure that all procedures the subject would be expected to undergo are discussed in the document. OHRP also acknowledges that current UC IRB procedures requires a revision of the protocol and the consent form when substantive changes are made, and that expedited review of a modification that changes the population of subjects or a substantial increase in compensation will not be allowed. In addition, OHRP notes that

the IRB policy has been changed to require investigators to submit their five year updated protocol simultaneously with the progress report for the previous period.

OHRP acknowledges the UC IRB's concerns that other studies by this investigator may contain similar instances of non-compliance and that these studies are being audited.

(2) OHRP finds that the informed consent documents reviewed and approved by the IRB for this project failed to include an adequate description of the following elements required by HHS regulations at 45 CFR 46.116(a):

(a) Section 46.116(a)(1): A description of the procedures to be followed, and identification of any procedures which are experimental. For example, the following research procedures were not mentioned in the informed consent document:

(i) Psychological tests that would be administered to the subjects, except "I may be asked questions about any traumatic events that occurred in my life."

(ii) Discontinuation of psychoactive medications about 2 weeks prior to lumbar puncture and prescription of a "controlled low-monoamine diet for at least 3 days before admission...."

(iii) Fasting and abstaining from smoking for more than 20 hours.

(b) Section 46.116(a)(2): A description of the reasonably foreseeable risks and discomforts. Risks of the following procedures were not mentioned in the informed consent document:

(i) Psychological tests that would be administered to the subjects.

(ii) Discontinuation of psychoactive medications about 2 weeks prior to lumbar puncture.

(iii) Prescription of a controlled low-monoamine diet for at least 3 days before admission.

(iv) Fasting and abstaining from smoking for more than 20 hours.

(c) Section 46.116(a)(8): 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. The informed consent document stated that "...refusal to participate in this study will

not influence standard treatment for the subject." There could be penalties or loss of benefits other than influence on standard treatment.

Corrective Actions: OHRP acknowledges that the principle investigator has been made aware of the need to provide a complete description of the procedures and of the risks and benefits in the informed consent document, and that the IRB currently reviews consent forms to make certain they fully describe the procedures and risks. OHRP also notes that the current IRB standards for language regarding consequences of refusing to participate is consistent with the regulations.

(3) HHS regulations at 45 CFR 46.103(f) require that an institution with an approved assurance shall certify that each *application* for research has been reviewed and approved by the IRB. In July of 1994, the Principal investigator requested a change in the name of the protocol to include PTSD to "...be compatible with the title of a grant application...." OHRP finds that the IRB never reviewed this grant application.

Corrective Actions: OHRP acknowledges UC's report that all grant applications, including those submitted internally to the Veteran's Administration, are now required to be submitted to the IRB.

OHRP finds that the preceding corrective actions adequately address these 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.

(4) 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. Additionally, where the convened IRB specifies conditions for approval of a protocol that are to be verified as being satisfied by the IRB Chair or another IRB member designated by the Chair, the approval period must begin on the date the protocol was reviewed by the convened IRB, not on the date the IRB Chair or his or her designee verifies that IRB-specified conditions for approval have been satisfied.

OHRP notes that the IRB apparently failed to conduct continuing review of study 98-7-31-1at least once per year. Initial review for this study occurred September 9, 1998, continuing review occurred December 22, 1999, and the study was closed February 7, 2001.

If the IRB does not re-approve the research by the specified expiration date, subject accrual should be suspended pending re-approval of the research by the IRB. (Enrollment

of new subjects cannot ordinarily occur after the expiration of IRB approval. Continuation of research interventions or interactions in already enrolled subjects should only continue when the IRB finds that it is in the best interests of individual subjects to do so.)

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. Michael Walton, Medical Center Director, Chillicothe VAMC
Dr. Peter Frame, IRB Co-Chair, UC IRB-01/A
Dr. Frederick J. Samaha, MD, Chair, UC IRB-01/B
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