DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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January 26, 2006

William F. Owen, Jr., M.D.
Chancellor
University of Tennessee Health Science Center
62 S. Dunlap, Room 220
Memphis, TN 38163

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1056 and Federalwide Assurance FWA-2301

Research Project: Clinical Investigation on the Effects of Early Administration of Prolonged Methylprednisolone Therapy in Patients with ARDS (Early ARDS Study)
Principal Investigator: Umberto Meduri, M.D.

Research Project: Clinical Investigation on the Effects of Corticosteroid Therapy on the Proliferative Phase of Diffuse Alveolar Damage in Patients with Late ARDS (Late ARDS Study)
Principal Investigator: Umberto Meduri, M.D.

Research Project: Prospective, Double-Blind, Randomized Trial on the Effects of Low-Dose Hydrocortisone Infusion in Patients with Severe Sepsis (Sepsis Study)
Principal Investigator: Umberto Meduri, M.D.

Dear Dr. Owen:

The Office for Human Research Protections (OHRP) has reviewed the University of Tennessee Health Science Center's (UTHSC) January 26, 2005 response to OHRP's October 19, 2004 letter regarding allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46) involving the above-referenced research.

Based upon review of the UTHSC report, OHRP makes the following determinations:

(1) HHS regulations at 45 CFR 46.103(b) and 109(a) require that the IRB must review and approve all non-exempt human subject research covered by an assurance. OHRP finds that the principal investigator in the above-referenced research conducted ancillary studies related to (i) polymorphisms in inflammatory markers and mortality and (ii) pharmacokinetics of methylprednisolone in ARDS patients without institutional review board (IRB) review and approval. In specific, OHRP notes that the January 26, 2005 UTHSC report stated the following:

> (a) "Polymorphispm (genetic testing) in most of the Early ARDS population was completed prior to obtaining IRB approval and without informed consent of the patients."
>
> (b) "The blood samples for ½ of the patients (10/20) included in this study [Early ARDS] were obtained prior to IRB approval of this modification. There is no documentation that these patients signed a modified informed consent that gives permission to draw and analyze their blood for methylprednisolone."

(2) HHS regulations at 45 CFR 46.116 state that, except as provided elsewhere in the regulations, no investigator may involve a human being as a subject in research covered by the regulations unless the investigator has obtained the legally effective informed consent of the subjects or the subject's legally authorized representative. Based on the statements noted in item (1) above, OHRP finds that subjects were enrolled without the investigator obtaining the legally effective informed consent of the subjects or their legally authorized representative.

(3) HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the IRB review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects.

> (a) OHRP finds that the principal investigator enrolled a subject in the Sepsis Trial who did not meet the eligibility criteria and that the UTHSC IRB failed to review and approve this change to the protocol. In specific, OHRP notes the following:
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> > The January 26, 2005 UTHSC report stated, "Patient #77 was entered in the Sepsis Trial against the criterion of the approved IRB protocol."
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> (b) It was alleged that the principal investigator failed to properly implement the cross-over provision in the Late ARDS trial protocol. OHRP is unable to find evidence to substantiate this allegation.

(4) It was alleged that the Early ARDS trial failed to ensure that risks to subjects were minimized, in part, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, as required by HHS regulations at

45 CFR 46.111(a)(1). It had been alleged that because falsified data from the Late ARDS trial was utilized to justify proceeding with the Early ARDS trial, this second trial should not have been initiated. It was also alleged that the Data Safety and Monitoring Board (DSMB) for the Early ARDS trial was concerned that principal investigator was retrospectively declaring subjects ineligible in an attempt to conceal serious side effects of the intervention.

Regarding the falsification of data, OHRP notes that the UTHSC has provided opinions from consultants indicating that, although discrepancies exist between the study protocol, the research database and a report published in the Journal of the American Medical Association, the principal investigator did not commit scientific misconduct. In addition, regarding the DSMB's concern that the investigator was retrospectively declaring subjects ineligible, a memo from the chair of the DSMB stated the following:

> "I can find no reference that we, the DSMB, were concerned that Dr. Meduri was retrospectively declaring patients ineligible in an attempt to conceal serious side effects of the intervention."

Due to the conflicting nature of the allegations and the UTHSC report, OHRP is unable to make a determination regarding the allegations noted under item (4), above.

(5) It was alleged that the UTHSC failed to promptly report the suspension of the Early ARDS in November of 2001 to OHRP, as required by HHS regulations at 45 CFR 46.(103)(a) and 46.103(b)(5). The UTHSC report indicated that approval for the Early ARDS trial had expired after the principal investigator failed to meet the deadline for the submission of continuing review materials. The UTHSC IRB sent a letter to the principal investigator on October 16, 2001 indicating that no new subjects could be enrolled in the study until the IRB could conduct its continuing review. OHRP does not consider expiration of IRB approval to constitute a suspension or termination of IRB approval.

OHRP finds that this allegation could not be substantiated.

Corrective Actions: OHRP acknowledges the following corrective actions undertaken by the UTHSC:

(a) The UTHSC Office of the Vice Chancellor for Research has staffed a new Office of Human Subject Protections which is responsible for education of faculty, investigators, and others involved in human subjects research.

(b) The UTHSC IRB has been provided funds to conduct random audits of IRB-approved research with an emphasis on high risk studies.

(c) The IRB will send an e-mail to all investigators to remind them of their responsibilities of requesting IRB approval for changes in already approved

research. In addition, the Office of Human Subject Protections will increase its educational efforts with respect to the regulatory requirement for instituting changes to already approved research.

(d) The UTHSC IRB will institute a stored tissue audit policy that will be conducted at least annually on all studies utilizing human tissues. The results of these audits will be reviewed by the Office of Human Subject Protections at UTHSC.

(e) The principal investigator for the above-referenced research will be advised that deviations from the approved research protocols were found and that prior approval for changes must be obtained from the IRB.

(f) The principal investigator will be informed that the results of the polymorphism testing which were performed on subjects without their consent may not be considered and may not be used for purposes of presentation and/or publication.

OHRP finds that these corrective actions adequately address the above determinations and are appropriate under the institution's assurance. As a result of this determination, OHRP anticipates no further involvement in this matter.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Patrick J. McNeilly, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Leonard Johnson, Vice Chancellor for Research, UTHSC
Dr. Clair Cox, Chair, UTHSC IRB #1 and #2
Dr. Gary Smith, Chair, UTHSC IRB #3
Dr. John Morgan, Chair, UTHSC IRB #4
Commissioner, FDA
Dr. David Lepay, FDA
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