DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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July 22, 2004

Barbara C. Pence, Ph.D.
Associate Vice President for Research
Associate Dean for Research and the Graduate School
Texas Tech University Health Sciences Center
Office of Research
3601 4th Street, Stop 6206
Lubbock, Texas 79430-6206

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1078 and Federalwide Assurance (FWA) 6767

Research Project:	Multi-Center, Double-Blind, Placebo Controlled, Randomized, Phase 3 Study of Tifacogin [Recombinant Tissue Factor Pathway Inhibitor (rTFPI/SC-597350)] in Severe Sepsis TFP007
Principal Investigator:	Thomas C. Butler, M.D.
Protocol Number:	IRB # 00091

Research Project:	Treatment of Plague with Gentamicin or Doxycycline
Principal Investigator:	Thomas C. Butler, M.D.
Protocol Number:	IRB # 02215

Research Project:	Treatment of Septic Shock with Urokinase
Principal Investigator:	Robert M. Hardaway, M.D.

Research at Thomason Hospital

Dear Dr. Pence:

The Office for Human Research Protections (OHRP) has reviewed Texas Tech University Health Sciences Center's (TTUHSC) March 27, 2003 and February 23, 2004 reports that were submitted in response to OHRP's January 30, 2003 letter to TTUHSC, regarding allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR Part 46) involving the above-referenced research.

Based upon its review of TTUHSC's March 27, 2003 and February 23, 2004 reports, as well as additional documentation submitted by TTUHSC on May 12, 2004, OHRP makes the following determinations regarding the above-referenced research:

(1) In its January 30, 2003 letter, OHRP presented allegations that Dr. Butler conducted human subject research during the TTUHSC IRB suspension of all of his human subject research; and that Dr. Butler obtained samples from IRB protocol #02215 prior to TTUHSC IRB review and approval, in contravention of HHS regulations at 45 CFR 46.103(b) and 46.109(a). In addition, it was alleged that the TTUHSC IRB was unaware of the existence of these samples when IRB protocol #02215 was reviewed by the IRB, and therefore the TTUHSC IRB appeared to lack sufficient information to make the determinations required for approval of this research under HHS regulations at 45 CFR 46.111.

TTUHSC's February 23, 2004 report stated the following:

> "...it has since been established through testimony in the recent federal trial of Dr. Butler, that he had not received IRB review and approval for the protocol (#02215) referenced hereinabove, nor did he respond to the IRB when it questioned him concerning his involvement in that protocol. It has also been determined that he was collecting data from the unauthorized Tanzanian trial and conducting a data analysis for a consulting agreement with the FDA, which was negotiated outside the knowledge and without authorization of the TTUHSC Office of Sponsored Programs, that was ultimately consummated in January 2003. This unsanctioned action occurred after Dr. Butler had been suspended from conduct of all clinical research by the TTUHSC IRB on November 6, 2002. Dr. Butler was convicted of 47 counts, most of them involving fraud and deception against TTUHSC. Prior to his sentencing...a settlement agreement was negotiated between TTUHSC and Dr. Butler resulting in his retirement from TTUHSC...Unrelated to the settlement with TTUHSC, Dr. Butler recently

> relinquished his medical license and is no longer practicing medicine or performing clinical trials..."

Based on the information above, OHRP finds that Dr. Butler obtained samples from IRB protocol #02215 prior to TTUHSC IRB review and approval, and that he conducted human subject research during the TTUHSC IRB suspension of all of his human subject research. OHRP also finds that, due to Dr. Butler's failure to provide information regarding the collection of samples prior to his request for IRB approval of protocol #02215, the TTUHSC IRB was unaware of the existence of these samples when IRB protocol #02215 was reviewed by the IRB.

Corrective action: OHRP acknowledges that Dr. Butler is no longer associated with, practicing medicine at or performing clinical trials at TTUHSC. OHRP also acknowledges that final IRB approval of protocol #02215 was not granted. OHRP notes that TTUHSC's revised IRB policies and procedures dated February 26, 2004 (Procedures) state that principal investigators, co-investigators, and all research staff are required to receive initial and continuing training regarding the protection of human subjects in research.

(2) HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5) require that institutions promptly report to OHRP any serious or continuing noncompliance with 45 CFR part 46 or the requirements or determinations of the IRB, and any suspension or termination of IRB approval. It was alleged that the suspension of IRB approval of all of Dr. Butler's research was not promptly reported to OHRP.

TTUHSC's March 27, 2003 report stated the following:

> "Due to the PI's non-response to the IRB request for information on protocol #00091, the IRB suspended all human research by the PI on October 23, 2002. The transition of leadership within the office of the Associate Vice President for Research and the appointment of a new IRB Chair on January 1, 2003 delayed notification to OHRP and FDA. Upon discovering the oversight, a notification letter was sent by overnight delivery to OHRP and the FDA on February 13, 2003."
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> "Protocol #02215 was reviewed by the IRB on August 28, 2002. The protocol was accepted pending clarification, and the PI was notified of the need for additional information on September 4, 2002. Although action was taken by the IRB during the same meeting to suspend enrollment of new subjects in all of the PI's active protocols, it was felt the PI would promptly provide information that

> would allow resumption of enrollment in all of the PI's studies. The PI did not respond to the request for further information, however, and protocol #02215 was removed from consideration by the IRB. The PI was notified on October 4, 2003, but it was assumed that OHRP notification of the IRB action removing the protocol from consideration was not required."

With regard to IRB protocol #00091, OHRP finds that TTUHSC failed to promptly report to OHRP the IRB suspension of all human subject research by Dr. Butler on October 23, 2002. With regard to IRB protocol #02215, OHRP notes that since Dr. Butler failed to provide the requested information to the IRB, final IRB approval of this uninitiated protocol was not granted. Such rescission of an IRB contingency-based approval for an uninitiated research protocol does not need to be reported to OHRP as a suspension of IRB approval under HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

Corrective action: OHRP acknowledges TTUHSC's February 13, 2003 letter to OHRP regarding the IRB suspension of all human subject research by Dr. Butler on October 23, 2002. OHRP notes that TTUHSC's IRB Procedures now require the Associate Vice President for Research to promptly report suspension or termination of research to OHRP. Further, OHRP notes that TTUHSC's IRB Procedures now require that if a study has been suspended by the IRB for any reason, the principal investigator shall not submit any proposed studies for IRB review until the suspension has been resolved.

(3) HHS regulations at 45 CFR 46.107(e) state that no IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest. It was alleged that the IRB Chair, Dr. Melvin Laski, who was a close friend of Dr. Butler, encouraged the IRB to approve protocol #02215.

(a) TTUHSC's March 27, 2003 report stated the following:

> "A memo addressed to the IRB by Dr. Barbara Pence, Associate Vice President for Research, requested that the IRB Chair recuse himself during consideration of an audit report of Dr. Thomas Butler's protocol #00091. This request was based on a previous conversation between Dr. Pence and Dr. Laski, in which he has expressed that the friendship between Dr. Laski's wife and Dr. Butler's wife placed him in an uncomfortable position. The IRB Chair recused himself during the discussion of the audit report and left the room. He returned for the rest of the meeting which included consideration of a new protocol #02215 submitted by Dr. Butler. The IRB Chair does not typically vote, and in this case Dr. Laski

> did not vote on protocol #02215. On October 7, 2002, Dr. Laski was counseled by Dr. LaJean Chaffin, Acting Associate Vice President for Research, on the appearance of conflict of interest in recusing himself in one case but not the other."

(b) A July 29, 2002 memorandum from Dr. Pence to the TTUHSC IRB regarding the clinical audit of protocol #00091 stated the following:

> "I have received the final report of the clinical audit of Dr. Thomas Butler's IRB Protocol 00091, which I had requested on March 1, 2002... I am submitting this report to the IRB for their decision as to any further action needed, and ask that Dr. Laski recuse himself from the deliberation because he has previously stated to me that his wife and Butler's were good friends and that the situation placed him in an uncomfortable position."

OHRP acknowledges that, based upon Dr. Laski's admission of a close social relationship with Dr. Butler, Dr. Pence specifically requested the IRB to recuse Dr. Laski during the IRB's review of a clinical audit of protocol #00091 that reported violations of HHS regulations and TTUHSC's policies. Since Dr. Pence had made the determination that Dr. Laski had a potential or actual conflict of interest that needed to be eliminated by prohibiting Dr. Laski from involvement in IRB deliberations concerning Dr. Butler, OHRP finds that the IRB also should have recused Dr. Laski from participation in the IRB's review of protocol #02215.

Furthermore, OHRP acknowledges Dr. Laski's resignation as IRB Chair in December 2002. OHRP notes that TTUHSC's IRB Procedures now recognize that a conflict of interest may exist if an IRB member has a personal relationship with the principal investigator or strong positive or negative interactions that may be perceived as a possible conflict of interest.

(4) It was alleged that protocol changes were implemented by Robert Hardaway prior to obtaining IRB review and approval, in contravention of HHS regulations at 45 CFR 46.103(b)(4)(iii). In specific, it was alleged that Dr. Hardaway used up the study drug (urokinase) for the above-referenced research project, and substituted another drug prior to obtaining IRB review and approval. Additionally, it was alleged that this study drug substitution resulted in harm to or even the death of a subject.

TTUHSC's March 27, 2003 report stated the following:

> "There were two deviations from protocol associated with Dr. Robert Hardaway's IRB approved urokinase study. These included:
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> • Multiple infusions of the study drug when only one infusion was listed in the protocol approved by the IRB
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> • In one case, a drug not listed on the protocol, streptokinase, was administered when urokinase was the only drug listed for the study."
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> "Internal investigation also raised questions regarding hospital privileges and lack of signed informed consent [for] study subjects."
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> "During an internal audit in February 2002, it was determined that the death of a subject on January 4, 1991 (Case #2) had not been reported to the TTUHSC-El Paso IRB, OHRP, or the FDA. In this fatal case, the patient's death appeared to be a result of cardiac complications rather than bleeding attributed to the study drug; however, this is under further investigation. Urokinase was the only study drug administered to the patient, but two infusions of the drug were given. Since only one infusion was approved by the IRB and FDA, this was a deviation from the protocol."

Based on the information above, OHRP finds that the protocol changes and study drug substitution by Dr. Hardaway were implemented prior to his obtaining IRB review and approval. OHRP was unable to make a determination regarding the allegation that the study drug substitution resulted in harm to or even the death of a subject.

Corrective action: OHRP acknowledges TTUHSC's suspension of Dr. Hardaway's research in April 1999 and Dr. Hardaway's termination with the faculty of the TTUHSC on August 31, 1999. OHRP notes that TTUHSC has established a Human Subjects Protection Office that is responsible for compliance activities, including audits and monitoring of IRB-approved research involving human subjects on behalf of TTUHSC and the IRB.

OHRP finds that the corrective actions summarized above adequately address the above determinations and are appropriate under the TTUHSC Assurance. As a result, there should be no need for further involvement of OHRP in this matter. However, OHRP must be notified should new information be identified which might alter this determination.

OHRP has the following additional comments:

(5) OHRP finds that TTUHSC has adequately addressed additional concerns raised by OHRP regarding research activities at Thomason Hospital.

(6) Based upon findings of noncompliance discovered during a retrospective clinical audit of IRB protocol #00091, the TTUHSC IRB suspended enrollment on all of Dr. Butler's active protocols on August 28, 2002, pending Dr. Butler's response to the findings of TTUHSC IRB's clinical audit. In its January 30, 2003 letter, OHRP presented the allegation that Dr. Butler had not responded adequately to the TTUHSC IRB findings of noncompliance.

TTUHSC's March 27, 2003 report stated the following:

> "A clinical audit requested by the Associate Vice President for Research, Barbara C. Pence, Ph.D., was conducted to clarify information regarding the reporting of Adverse Events during the study. Information obtained from this audit was presented to the IRB on August 28, 2002, and based upon several apparent deviations from protocol and concern over potential subject safety, the IRB suspended the enrollment of subjects on all active protocols for the PI. The PI was notified of the IRB action and given appropriate time to respond to the issues of non-compliance that were discovered during the clinical audit. The PI did not respond to this request, and on November 6, 2002 the IRB suspended his privileges to conduct human research."

OHRP acknowledges the TTUHSC IRB's November 6, 2002 suspension of Dr. Butler's privileges to conduct human subject research at TTUHSC as a result of Dr. Butler's failure to respond to clinical audit findings of noncompliance. Such action is appropriate under the TTUHSC Assurance.

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

Sincerely,

Robert J. Meyer
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. M. Roy Wilson, President, TTUHSC
Dr. Roderick Nairn, Executive Vice President for Academic Affairs, TTUHSC
Dr. Sandra M. Whelly, Chair, IRB #1, TTUHSC
Dr. Brian Pruitt, Chair, IRB #2, TTUHSC
Dr. Paul Casner, Chair, IRB #3, TTUHSC
Commissioner, FDA
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Dr. Bernard A. Schwetz, OHRP
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Dr. Michael A. Carome, OHRP
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Ms. Shirley Hicks, OHRP
Ms. Jan Walden, OHRP
Ms. Melinda Hill, OHRP
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