DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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May 17, 2006

William F. Owen, Jr., M.D.
Chancellor
The University of Tennessee Health Science Center
62 South Dunlop Street
Memphis, TN 38163

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

Research Project: A Clinical Trial of Two Medications on Smoking Cessation ("STAR Study")
Principal Investigator: Karen C. Johnson, M.D., M.P.H.
HHS Grant Number: R01 HL066025

Dear Dr. Owen:

The Office for Human Research Protections (OHRP) has reviewed the University of Tennessee's (UT) May 19, 2005 report regarding allegations of noncompliance with the Department of Health and Human Services (HHS) regulations protecting human research subjects at 45 CFR Part 46 concerning the above-referenced UT research project (hereinafter referenced as "STAR Study").

OHRP makes the following findings about the above research:

(1) HHS regulations at 45 CFR 46.111(a)(1) require that IRBs, in order to approve research, determine that risks to subjects (including financial risks) are minimized. HHS regulations at 45 CFR 46.111(a)(7) require that IRBs, in order to approve research, determine that there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. OHRP received allegations that in order to receive compensation for clinic visits in the STAR study, subjects were required to provide their names and social security numbers in a log visible to others.

OHRP acknowledges UT's statement that prior to July 8, 2004, subjects provided their name and social security number in a record of incentive payments that was available to other subjects signing the same sheet. OHRP finds that this system for recording payments made to subjects neither minimized financial risk, nor adequately protected

subjects' privacy.

Corrective Action: Following an IRB compliance audit on July 8, 2004, the procedure for recording subject payments was changed to (1) cover the names of individuals who have already signed the record when additional subjects sign the form, and (2) research staff add social security numbers to the payment record at the end of the day, so subjects or others accompanying them on visits cannot view other subjects' social security numbers. OHRP finds that these corrective actions adequately address the above findings and are appropriate under the UT FWA.

(2) HHS regulations at 45 CFR 46.109(a) grant IRBs the authority to require modifications in research. OHRP acknowledges UT's finding that a research coordinator gave outdated consent documents to 31 STAR subjects, which did not include (a) an amendment approved by the UT IRB on May 25, 2004 describing a voluntary blood repository (participation in which was not a requirement for participation in the STAR study) and (b) a separate consent form to participate in the blood repository also approved by the IRB on May 25, 2004.

Corrective Action: The consent forms approved on May 25, 2004 were put into use immediately after an IRB audit in July 2004 confirmed that subjects enrolled between May and July received outdated consent forms and did not receive the separate repository consent. These subjects were provided additional informed consent using the May 25, 2004 consent documents. Subjects who remained in the study after randomization were given the updated consent documents in person. Subjects who did not remain in the study after receiving the outdated consent documents were sent copies of the updated documents by mail. OHRP finds that these corrective actions adequately address the above findings and are appropriate under the UT FWA.

(3) HHS regulations at 45 CFR 46.116(a)(1) require that informed consent documents contain a description of any procedures to be followed, and identification of any procedures which are experimental, in a language understandable to all subjects. OHRP finds that the STAR main study consent form and separate STAR Blood Repository consent form each approved by the IRB on May 25, 2004, do not describe all medical or research procedures in a manner that would be understandable to the target STAR population of young, low income smokers. For example:

> (a) Without defining "Nicotine Replacement Therapy (NRT)" or "sustained release bupropion (Zyban)" the main consent form informs subjects that the purpose of the research study is to assess their effects in helping smokers stop smoking. In addition, neither the main study nor blood repository consent form defines what a blood repository is.
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> (b) The main consent form does not notify potential subjects about procedures that researchers employ to track down subjects who fail to attend follow-up clinic visits. The STAR Standard Operating Procedures (SOPs) describe the following escalating plan for locating subjects. First, study staff call and write to subjects

directly. If these methods fail to locate subjects, study staff call contacts given by subjects to ascertain any new phone number or address, or use internet searches. As a last resort, the Cole Reverse Directory is used to identify neighbors of subjects who are then called in an effort to determine if subjects have moved and how they might be contacted.

(c) The main consent form does not clarify whether data collected on subjects who do not complete follow-up visits will remain part of the study.

Required Corrective Action: Please submit to OHRP a corrective action plan to address the findings in (3)(a) through (c) and to ensure that informed consent documents approved by the IRB include a complete description of all research procedures in a manner understandable to STAR subjects.

(4) HHS regulations at 45 CFR 46.116(a)(7) require that the following information be provided to subjects in the informed consent process:

> An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

The IRB-approved STAR informed consent document identifies Dr. Karen Johnson as the individual to contact for after-hours questions or in the event that subjects experience any injury as a result of the study. OHRP finds that this information is inaccurate. STAR SOPs clarify that subjects calling after hours are routed to an on-call nurse. If there are unanswered questions or unresolved issues, subjects are then given access to an on-call physician. Only in the event that the on-call nurse and the on-call physician are unable to resolve a subject's concerns is Dr. Karen Johnson contacted.

Required Corrective Action: Please submit to OHRP a corrective action plan to address the finding in (4).

(5) HHS regulations at 45 CFR 46.116(a)(2) require, as part of the informed consent process, that subjects be provided a description of any reasonably foreseeable risks or discomforts that could result from participating in research.

(a) OHRP finds that the STAR informed consent form failed to inform potential subjects that the combined effect of NRT and Zyban could increase blood pressure. OHRP notes that the impact of this omission may have been exacerbated by the fact that the informed consent form referenced one study examining the combined effects of NRT and Zyban which found no increase in adverse events when compared to treatment with either drug alone, and stated that "[g]iven this experience, we also do not expect increased adverse effects with the combination therapy."

(b) OHRP finds that the facts do not support allegations that the informed consent

document failed to describe increased risk of suicide as a side effect of Zyban. OHRP acknowledges UT's statement that STAR investigators reviewed whether to amend the informed consent document when FDA issued a Public Health Advisory on suicidal ideations in children and adolescents with Major Depressive Disorder and other psychiatric disorders. Since STAR subjects are adults pre-screened for depression and depressed mood, the information in the FDA advisory does not represent a reasonably foreseeable risk requiring alteration of the informed consent form.

Corrective Action: The STAR investigators submitted the following informed consent amendment to the UT IRB for approval:

> High blood pressure, in some cases severe, has been reported in persons taking Zyban alone and in combination with nicotine replacement therapy. As a precaution your blood pressure will be monitored at each study visit and the study medications may be stopped if you develop high blood pressure.

OHRP finds that this corrective action adequately addresses the findings in (5)(a) and is appropriate under the UT FWA.

(6) OHRP finds that the allegation that subjects were enrolled in the above protocol after the IRB reviewed and approved a draft protocol but before final IRB approval is not supported by the evidence supplied to OHRP. OHRP acknowledges UT's statement that the protocol which received final IRB approval on July 11, 2002 was the protocol in place when subjects were enrolled. No signed consent forms or other evidence was presented to OHRP indicating that subjects were enrolled in the research prior to July 11, 2002.

OHRP has the following additional questions and concerns about the above research:

(7) [Redacted]

[Redacted]

Please submit to OHRP by June 15, 2006 a corrective action plan to address the findings in paragraphs (3) and (4) above, as well as the questions and concerns in paragraph (7).

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

Sincerely,

Carol J. Weil, J.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Michael E. Dockter, Vice Chancellor for Research, UT
Dr. Clair E. Cox, Chair, UT IRBs 1 and 2
Dr. Joseph E. Fuhr, Chair, IRB 3
Dr. John Morgan, Chair, IRB 4
Dr. Karen Johnson, UT
Dr. Amando Freire, UT
Dr. Tom Puglisi, ORO, Department of Veterans Affairs
Dr. Lana Skirboll, Office of Science Policy, NIH
Dr. Bernard Schwetz, OHRP
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Ms. Shirley Hicks, OHRP
Ms. Pat El-Hinnawy, OHRP
Ms. Janet Fant, OHRP
Commissioner, FDA
Dr. David Lepay, FDA