DEPARTMENT OF HEALTH & HUMAN SERVICES

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J. Reid Jones, Ph.D.
IRB Chairperson/Academic Research Coordinator
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RE: Human Research Subject Protections Under Federalwide Assurances FWA- 1198

Research Project: Phase III Randomized Study of Selenium and Vitamin E for the Prevention of Prostate Cancer– SELECT
Project Number: SWOG-S0000
Principal Investigator: **Nathaniel Brown, M.D.**

Dear Drs. Brown and Jones:

The Office for Human Research Protections (OHRP) has reviewed the Mid-Delta Family Practice Clinic's (MDFPC) January 18, 2006 and Delta State University institutional review board's (DSU IRB) January 16, 2006 report responding to determinations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46). OHRP notes that MDFPC has currently designated only the DSU IRB for review of research covered by the MDFPC FWA.

In its December 13, 2005 letter, OHRP made the following determinations regarding human subjects protections at MDFPC and DSU IRB:

> (1) OHRP found that neither MDFPC nor its designated IRB, the DSU IRB, have written IRB procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5):

(a) The procedures which the IRB will follow for conducting its initial review of research.

(b) The procedures which the IRB will follow for conducting its continuing review of research.

(c) The procedures which the IRB will follow for reporting its findings and actions to investigators and the institution.

(d) The procedures which the IRB will follow for determining which projects require review more often than annually.

(e) The procedures which the IRB will follow for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review.

(f) The procedures which the IRB will follow for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

(g) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, any department or agency head, and OHRP of: (a) any unanticipated problems involving risks to subjects or others; (b) any serious or continuing noncompliance with 45 CFR part 46 or the requirements or determinations of the IRB; and (c) any suspension or termination of IRB approval.

Corrective Action: OHRP acknowledges that the MDFPC plans to engage the services of an independent IRB, and that the DSU IRB has decided to withdraw as the IRB for MDFPC, agreeing to serve on a temporary basis until they are able to establish a relationship with a new IRB. OHRP also acknowledges that the DSU IRB did not send all the IRB written procedures initially, and has revised those procedures. However, OHRP recommends that the DSU procedures be further revised (please see OHRP guidance at http://www.hhs.gov/ohrp/humansubjects/guidance/irbgd702.htm for developing IRB written procedures) to more fully address the following:

(a) The procedures which the IRB will follow for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review.

(b) The procedures which the IRB will follow for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has

already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

(c) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, any department or agency head, and OHRP of any suspension or termination of IRB approval.

(2) HHS regulations at 45 CFR 46.116(a)(2) require that when seeking informed consent for the research, subjects be provided with an adequate description of the reasonably foreseeable risks and discomforts. OHRP found that subjects were not informed in a timely manner of new findings of selenium toxicity. In specific, these new findings were communicated to Dr. Brown by October 2004; however, your September 14, 2005 report to OHRP indicates that this letter was not approved by the IRB until March 31, 2005 and was not distributed to subjects until after March 31, 2005.

Corrective Action: OHRP acknowledges that MDFPC has entered into a mentoring program with input from a nearby university, which has already resulted in some changes to MDFPC procedures. These include procedures to ensure that updates and correspondence from sponsors will be submitted to the IRB within 48 hours, and delegation of management of IRB submissions and correspondence to the head Clinical Research Associate (CRA) and a part-time data manager to be hired. The principal investigator will review these with the staff at bi-weekly meetings prior to there submission.

(3) HHS regulations at 45 CFR 46.115(a)(2) require, among other things, that minutes of IRB meetings be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining. OHRP found that DSU IRB minutes fail to meet these requirements. In addition, OHRP was not able to locate minutes from the IRB meeting held April 22, 2003.

Corrective Action: OHRP acknowledges DSU's statement that the DSU IRB will have a designated secretary in all meetings and that votes will be reported in the manner required by the HHS regulations at 45 CFR 46.115(a)(2). OHRP notes that the minutes of the January 17, 2006 DSU IRB meeting recorded the votes appropriately.

OHRP makes the following additional determinations:

(4) HHS regulations at 45 CFR 46.103(b)(4)(iii) require the IRB to 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. The Southwest Oncology Group (SWOG) audit indicates that 4 of 25 participants whose records were audited were not eligible to be enrolled (one had elevated blood pressure and three were taking Plavix plus a high dose of aspirin.) The investigator failed to seek and obtain IRB review and

approval to enroll ineligible subjects prior to their enrollment.

Corrective Action: OHRP acknowledges that MDFPC will review all participant records and all those found to be ineligible will no longer receive study supplements but will be followed until the end of the study. They will be informed of this in person and in writing. After approval of the most recent informed consent document by the new IRB, all eligible subjects will be contacted and informed consent sought.

(5) OHRP finds that the DSU IRB failed to conduct continuing review at least once per year, as required by HHS regulations at 45 CFR 46.109(e). SELECT records indicate that the protocol was reviewed by the DSU IRB May 3, 2001 and again September 13, 2002. OHRP finds that there was a more than four month lapse in approval of this protocol.

Corrective Action: OHRP acknowledges MDFPC's statement that a timeline and calendar of submission dates will be developed by the head CRA and followed closely to avoid a reoccurrence of this problem. OHRP also acknowledges that the DSU IRB will not serve as the IRB for any externally operated research or medical research until staffing allows the IRB to remind investigators in advance when they need to submit protocols for continuing review.

(6) 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. OHRP finds that the informed consent documents approved by the DSU IRB for this study did not appear to allow participants to indicate whether or not they wished to participate in the optional studies involving storage of toenails and blood for future research. The model informed consent document included check-off boxes for subjects to indicate their desire to take part (or not) in these optional studies, along with a supplemental information sheet. The DSU IRB-approved informed consent document for this study did state these studies were optional but did not have any mechanism for subjects to indicate their desire to take part (or not) in these optional studies, nor did it include the supplemental information.

Corrective Action: OHRP acknowledges MDFPC's statement that the revised informed consent document will include check-off boxes for subjects to indicate their desire to take part (or not) in these optional studies, along with a supplemental information sheet. Please ensure that all subjects who already had samples collected for this future research are given the supplemental information.

OHRP finds that the corrective actions taken adequately address the findings and are appropriate under the MDFPC FWA. As a result of this determination, 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.

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

Sincerely,

Kristina C. Borror, Ph.D.
Director
Division of Compliance Oversight

cc: Commissioner, FDA
Dr. David Lepay, FDA
Dr. Lana Skirboll, Director, Office of Science Policy, NIH
Ms. Joan Mauer, CTEP, NCI, NIH
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Ms. Shirley Hicks, OHRP
Dr. Irene Stith-Coleman, OHRP
Ms. Janet Fant, OHRP
Ms. Patricia El-Hinnawy, OHRP