DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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Albert L. Walker, Ed.D.
President
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RE: Human Research Subject Protections Under Federalwide Assurance (FWA) 10457

Research Project:	Socio-Cultural Determinants of Utilization of Breast Cancer Awareness and Prevention Services Among African-American Women in Southern West Virginia
Principal Investigator:	Anthony T. Woart, Ph.D.
Research Project:	Characterization of Molecular Diversity of HIV SUB-Types and Inter-Subtypes Recombinants Among African-Americans
Principal Investigator:	Edward Omolo, Ph.D.
Research Project:	Identification of at Risk African-American Adolescents for Type 2 Diabetes and the Role of Screening in Early Detection[1]
Principal Investigator:	Martha Eborall, Ph.D.
HHS Grant Number:	**RFA-MD-04-002/1R24 MD001107-01**

[1] OHRP notes that one of the studies identified in the initial grant application - Characterization of Molecular Diversity of HIV SUB-Types and Inter-Subtypes Recombinants Among African-Americans - differs from one of the studies identified in the grant progress report - Identification of at Risk African-American Adolescents for Type 2 Diabetes and the Role of Screening in Early Detection. OHRP assumes that the HIV Study was replaced by the Type 2 Diabetes Study. This assumption is based on a note found in a BSC document which states that the HIV study was cancelled because the investigator left BSC.

Dear Dr. Walker:

The Office of Human Research Protections (OHRP) has reviewed Bluefield State College's (BSC's) August 23, 2006 letter in response to OHRP's August 11, 2006 letter regarding allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR 46) involving the above-referenced research. Based on the information submitted, OHRP makes the following determination(s) regarding the above-referenced human subject research protocols:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.111 delineate the criteria that must be satisfied in order for an institutional review board (IRB) to approve research. OHRP finds that when initially reviewing the 3 studies referenced above, the BSC IRB lacked sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. Specifically, OHRP finds that the documentation upon which initial IRB approval was granted for all three studies contained little or no information regarding:

(a) Study purpose;
(b) Minimizing risks to subjects;
(c) Ensuring that risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result;
(d) Equitable selection of subjects (namely, subject recruitment and enrollment procedures);
(e) Informed consent (how sought and documented); and
(f) Provisions to protect the privacy of subjects and maintain the confidentiality of data.

(2) Continuing review of research must be substantive and meaningful. HHS regulations at 45 CFR 46.111 set forth the criteria that must be satisfied in order for the IRB to approve research. These criteria include, among other things, determinations by the IRB regarding risks, potential benefits, informed consent, and safeguards for human subjects. The IRB must ensure that these criteria are satisfied at the time of both initial and continuing review.

OHRP finds no evidence that the June 2006 continuing review of the Breast Cancer Study by the BSC IRB was substantive and meaningful. OHRP notes that the only documentation BSC provided to OHRP in reference to continuing review of the Breast Cancer Study in June 2006 consisted of a document entitled "Institutional Review Board Approval for Bluefield State College Minority Health Institute Center for Excellence Project EXPORT Socio-cultural determinants of Breast Cancer awareness and prevention Services among African-American Women in southern West Virginia, Grant 1 R24 MD001107-01; ***Principal Investigator: Martha Eborall Ph.D., MBA***" (emphasis added). The document

provided the following directive: "Please find attached ***abstract*** (emphasis added) for ***Dr. Woart's research proposal*** (emphasis added) as well as statement of the protection of human subjects involved in the study. Also please find attached approval Sheet for indication of your approval of the proposed protection of human subjects." OHRP finds that, based on the limited information provided to BSC IRB members, the IRB could not conduct substantial and meaningful continuing review.

OHRP also notes a discrepancy between the principal investigator listed in the document header and the principal investigator listed in the body of the document. There is no evidence that this inconsistency was identified by the IRB.

Moreover, OHRP finds no evidence that the October 2005 continuing review of the Type 2 Diabetes Study by the BSC IRB was substantive and meaningful. OHRP notes that BSC failed to provide documentation upon which the 2005 BSC IRB continuing approval was granted.

Required Action: Please provide OHRP with a corrective action plan outlining how BSC will ensure that the BSC IRB reviews sufficient information to make the determinations required for IRB approval, both at initial and continuing review, and that human subject research approved/re-approved by the BSC IRB satisfies the criteria outlined in 45 CFR 46.111.

(3) 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, but 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. While BSC provided documents listing two IRB approval dates for the Breast Cancer Study - an initial IRB approval date of April 7, 2004 and a continuing review IRB approval date of June 20, 2006 - BSC failed to provide documentation showing that the BSC IRB conducted continuing review of the Breast Cancer Study on or before April 7, 2005 (within one year of initial IRB approval). Thus, OHRP finds no documentation that the BSC IRB conducted continuing review of the Breast Cancer Study at least once per year as required by HHS regulations at 45 CFR 46.109(e).

Required Action: Please provide OHRP with a corrective action plan outlining how BSC will ensure that the BSC IRB conducts continuing review of non-exempt research at intervals appropriate to the degree of risk and not less than once per year.

(4) HHS regulations at 45 CFR 46.404-407 require specific findings on the part of the IRB for approval of research involving children. OHRP finds no evidence that the BSC IRB made the findings outlined in 45 CFR 46.404-407 when reviewing the Type 2 Diabetes Study, which involved children.

Required Action: Please provide OHRP with a corrective action plan outlining how BSC will ensure that human subject research involving children will only be approved by the BSC IRB if the research satisfies the criteria outlined in 45 CFR 46.404-407.

(5) 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. OHRP finds no documentation that the BSC IRB reviewed and approved the following protocol changes to the Breast Cancer Study prior to initiation:

(a) Use of a revised Breast Cancer Awareness and Prevention Program Baseline Participant Questionnaire (revised November 15, 2004); and
(b) Use of a revised Post-Intervention Breast Cancer Awareness and Prevention Program Baseline Participant Questionnaire (revised August 1, 2005).

Required Action: Please provide OHRP with a corrective action plan addressing how BSC will ensure prompt reporting to the BSC 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, are not initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

(6) HHS regulations at 45 CFR 46.103(f) require that an institution with an approved assurance certify that each *application* or proposal for research covered by the assurance has been reviewed and approved by the IRB. While BSC provided a grant application (RFA-MD-04-002) in response to OHRPs August 11, 2006 letter, OHRP finds no evidence substantiating that the BSC IRB reviewed the grant application prior to the initiation of research as required by HHS regulations at 45 CFR 46.103(f). In fact, OHRP notes that the following BSC documents provide evidence indicating that the BSC IRB did not review the grant application prior to initiation of the research:

(a) BSC IRB Polices and Procedures (dated May 25, 2004). Under the section titled Application Procedures, investigators are instructed "Please do not attach lengthy grant applications, etc., as the Board is unable to review them. The relevant information from such documents should be summarized in the *Request for Review*."
(b) Request for Review by the BSC Committee for the Protection of Human Subjects Application Form (BSC IRB Application). Under item 4, investigators are instructed not to attach lengthy grant proposals, etc. See item 4.

Required Action: Please provide OHRP with a corrective action plan outlining how BSC will ensure that the BSC IRB reviews and approves all grant applications involving human subject research covered by an HHS assurance.

(7) HHS regulations at 45 CFR 46.115(a) provides that an institution, or when appropriate an IRB, shall prepare and maintain adequate documentation of certain IRB activities. OHRP finds no evidence that the BSC IRB maintained the following documentation as required by HHS regulations at 45 CFR 46.115(a):

(a) Copies of the Type 2 Diabetes research proposal/grant application;
(b) IRB approved sample consent documents, progress reports and reports of injuries to subjects, if any, relating to the Breast Cancer Study;
(c) IRB approved sample consent documents, progress reports and reports of injuries to subjects, if any, relating to the HIV Study;
(d) Progress reports and reports of injuries to subjects, if any, relating to the Type 2 Diabetes Study;
(e) Minutes of IRB meetings at which the Breast Cancer Study, HIV Study and Type 2 Diabetes Study were reviewed and approved;
(f) Records of all continuing review activities for the Breast Cancer Study and Type 2 Diabetes Study; and
(g) Copies of all correspondence between the IRB and the investigators for the Breast Cancer Study, HIV Study and Type 2 Diabetes Study.

As a result of this lack of documentation, it was difficult for OHRP to reconstruct a complete history of all IRB actions related to the review and approval of the studies referenced above. In all instances, OHRP could not determine what the BSC IRB actually approved.

Corrective Action: BSC made the following statement in its August 23, 2006 response:

> "Poor documentation of the IRB review process, including lack of minutes of board meetings. The college has taken action to address this problem, including proving [sic] oversight of BSC IRB activities by Director of BSC Institutional Research and Effectiveness"

Required Action: Please provide OHRP with the above-referenced corrective action plan. Please provide a written detailed description of the specific actions taken to improve documentation of the IRB review process. In addition, please provide the IRB approved informed consent documents for the Breast Cancer Study and the HIV study. Lastly, please provide a copy of the minutes of the most recent BSC IRB meeting.

(8) HHS regulations at 45 CFR 46.116(a) delineate specific elements required for informed consent. OHRP finds that the informed consent document submitted by

BSC for the Type 2 Diabetes Study failed to include the following elements as required by HHS regulations at 45 CFR 46.116(a):

(a) Section 46.116(a)(1): (i) A statement that the study involves research; (ii) an explanation of the purposes of the research; (iii) the expected duration of the subject's participation; and (iv) a complete description of the procedures to be followed, and identification of any procedures which are experimental.
(b) Section 46.116(a)(2): A description of any reasonably foreseeable risks and discomforts (i.e., [risks and discomforts not described]).
(c) Section 46.116(a)(3): A description of any benefits to the subject or others that may reasonably be expected from the research.
(d) Section 46.116(a)(4): A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
(e) Section 46.116(a)(5): A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.
(f) Section 46.116(a)(6): For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
(g) Section 46.116(a)(7): An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights (should include someone other than the investigator), and whom to contact in the event of a research-related injury to the subject.
(h) 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.

Please note that OHRP only made findings specific to the Type 2 Diabetes Study informed consent document, given that BSC failed to provide OHRP with informed consent documents for the Breast Cancer Study and the HIV Study.

Required Action: Please provide OHRP with a corrective action plan addressing how BSC will ensure that the BSC IRB approves informed consent documents that contain the elements required under 45 CFR 46.116, unless informed consent or documentation of informed consent is appropriately waived by the IRB**.** In addition, provide a copy of the revised IRB-approved informed consent document(s) for the Type 2 Diabetes Study. In your response, indicate what plans BSC has to contact subjects already enrolled in the Type 2 Diabetes study and provide them with the appropriate information required under HHS regulations at 45 CFR 46.116(a).

(9) HHS regulations at 45 CFR 46.116 prohibit any exculpatory language in informed consent through which the subject is made to waive, or appear to waive, any of the subject's legal rights. OHRP finds the following language in the Type 2 Diabetes Study informed consent documents to be exculpatory: "I release the EXPORT Center and its employees from any liability arising from the following medical tests: Fasting Blood Glucose and Blood Lipid Panel" and "The undersigned does hereby release Bluefield Regional Medical Center, its physicians, agents, and employees from any liability arising from the collection of the specimen to be tested, the tests performed thereon, or the disclosure of the test results to the undersigned's duly authorized representative thereof, or to the undersigned's parents or legal guardian."

Required Action: Please provide OHRP with a corrective action plan addressing how BSC will ensure that the BSC IRB approves informed consent documents that do not contain exculpatory language.

(10) HHS regulations at 45 CFR 46.107(e) stipulate that no IRB member may participate in the IRB's initial or continuing review of a project in which the member has a conflicting interest, except to provide information requested by the IRB. OHRP notes that James Volker is listed as an advisory committee member on the above-referenced grant. OHRP finds that James Volker, a BSC IRB member with a conflicting interest in the Breast Cancer Study, participated in the BSC IRB 2006 continuing review of that study in violation of HHS regulations at 45 CFR 46.107(e).

Required Action: Please provide OHRP with a corrective action plan addressing how BSC will ensure that no IRB member with a conflicting interest in a project will participate in the initial or continuing review of the project, except to provide information requested by the IRB.

Based on the information submitted, OHRP makes the following determination(s) regarding BSCs system for protecting human subjects:

(11) OHRP finds that BSC does not have written IRB procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(b)(4) and (5):

(a) Procedures the IRB will follow for conducting its initial review of research;
(b) Procedures the IRB will follow for conducting its continuing review of research;
(c) Procedures 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;

(d) 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.

OHRP reviewed BSC 's Policies and Procedures of the Institutional Review Board for the Protection of Human Subjects (dated May 25, 2004) and found no evidence of the above referenced written procedures as required by 45 CFR 46.103(b)(5).

OHRP also finds that BSC's written procedures regarding reporting of unanticipated risks does not satisfy HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5). For instance, OHRP notes that BSC's current policy only addresses reporting unanticipated problems involving risks to participants or others to the IRB; BSC's current procedure does not address prompt reporting of such unanticipated problems to appropriate institutional officials, any Department or Agency head, and OHRP. Moreover, BSC's current procedure does not address prompt reporting to the IRB, appropriate institutional officials, any Department or Agency head, and OHRP of: … (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.

Required Action: Please provide OHRP with the written procedures outlined above. Please refer to OHRP's Guidance on Written IRB Procedures, available at http://www.hhs.gov/ohrp/humansubjects/guidance/irbgd107.htm, when drafting the procedures.

Based on the information submitted, OHRP has the following questions and concerns regarding the human subject research protocols referenced above:

(12) [Redacted]

[Redacted]

(13) [Redacted]

(14) [Redacted]

[Redacted]

(15)[Redacted]

Based on the information submitted, OHRP has the following questions and concerns regarding BSCs system for protecting human subjects:

(16)[Redacted]

OHRP has the following additional concerns regarding the BSC ’s Policies and Procedures of the Institutional Review Board for the Protection of Human Subjects (dated May 25, 2004) (BSC Policies and Procedures document):

(17) [Redacted]

[Redacted]

(18) [Redacted]

(19) [Redacted]

(20) [Redacted]

(21) [Redacted]

(22) [Redacted]

Please submit your response to the above findings, questions and concerns so that OHRP receives them no later than May 1, 2007. If during your review you identify additional areas of noncompliance with HHS regulations for the protection of human subjects, please provide corrective action plans that have been or will be implemented to address the noncompliance.

Do not hesitate to contact OHRP if you should have any questions regarding this matter.

Sincerely,

Lisa A. Rooney, J.D.
Compliance Oversight Coordinator

cc: Dr. Tracey K. Anderson, Director of Institutional Research and Effectiveness, BSC
Dr. Shekhar Pradhan, Chair, BSC IRB
Dr. Anthony T. Woart, BSC
Dr. Sam Shekar, OER, NIH
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Ms. Shirley Hicks, OHRP
Dr. Irene Stith-Coleman, OHRP