DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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July 9, 2007

Albert L. Walker, Ed.D.
President
Bluefield State College
219 Rock Street
Bluefield, WV 24701

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 (hereinafter referred to as the Breast Cancer Study)
Principal Investigator:	Anthony T. Woart, Ph.D.
Research Project:	Characterization of Molecular Diversity of HIV Sub-Types and Inter-Subtypes Recombinants Among African-Americans (hereinafter referred to as the HIV Study)
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 (hereinafter referred to as the Type 2 Diabetes Study)
Principal Investigator:	Martha Eborall, Ph.D.
HHS Grant Number:	**RFA-MD-04-002/1R24 MD001107-01**[1]

Dear Dr. Walker:

[1] In a letter dated April 25, 2007, you clarified that the HIV Study, which was identified in the initial grant application, was replaced by the Type 2 Diabetes Study after the HIV Study investigator left Bluefield State College (BSC) in May 2004. Based on this clarification, coupled with the fact that the initial grant application does not reference the Type 2 Diabetes Study, the Office for Human Research Protections (OHRP) has concluded that the Type 2 Diabetes Study was not in existence as of the date that the initial grant application was signed, i.e., April 16, 2004.

The Office for Human Research Protections has reviewed Bluefield State College's April 25, 2007 letter, which was submitted in response to OHRP's March 20, 2007 letter. In addition, OHRP has taken into consideration the information that was provided to OHRP by BSC faculty and staff during a June 15, 2007 videoconference.

Based on all the information provided to OHRP to date, OHRP makes the following findings:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(a) require that each institution engaged in research which is covered by the HHS regulations at 45 CFR part 46 and which is conducted or supported by HHS must provide written assurance satisfactory to the Secretary of HHS that it will comply with the requirements set forth in these HHS regulations. OHRP receives and approves such assurances on behalf of the Secretary.

OHRP finds that prior to August 7, 2006, BSC engaged in non-exempt human subjects research under the above-referenced HHS grant award without submitting a written assurance to OHRP as required by HHS regulations at 45 CFR 46.103(a). Furthermore, on at least two occasions BSC cited to HHS a number (i.e., #3341) for its assurance when it held no such OHRP-approved assurance. See section 6 of the grant progress report for the above-referenced grant, signed May 31, 2005. Section 6 pertains to HHS certification of institutional review board (IRB) approval. See also section 6 of the grant progress report for the above-referenced grant, signed May 25, 2006.

(2) In accordance with HHS regulations at 45 CFR 46.103(b), 46.109(a), and 46.109(e), an IRB designated under an OHRP-approved assurance must review and approve all non-exempt human subject research conducted or supported by HHS and conduct continuing review of such research at least annually. Furthermore, HHS regulations at 45 CFR 46.103(f) require that an institution engaged in non-exempt human subjects research conducted or supported by HHS certify that the application or proposal for such research has been reviewed and approved by the IRB.

OHRP finds that, in addition to the failure to hold an OHRP-approved assurance as noted in finding (1) above, BSC did not have a duly constituted, functioning IRB until Fall 2006 at the earliest, and that a BSC IRB did not conduct initial or continuing review of the above-referenced research prior to Fall 2006 at the earliest, in contravention of the requirements of HHS regulations at 45 CFR 46.103(b), 46.109(a), and 46.109(e). OHRP bases this finding on information provided by BSC faculty and staff during the June 15, 2007 videoconference as well as information previously submitted by BSC in its August 23, 2006 and April 25, 2007 letters to OHRP.

Of note, OHRP interviewed four of the seven individuals who were identified as members of the BSC IRB on an IRB membership roster submitted to OHRP in November 2004; i.e., the only time BSC registered/updated its IRB with OHRP. During the videoconference, one of these individuals informed OHRP that s/he was

never a member of any BSC IRB; that BSC did not have an IRB until 2006, and that the IRB did not review research at a convened IRB meeting until Fall 2006. Another individual informed OHRP that s/he was not a member of any BSC IRB until Fall 2006; that BSC did not have an IRB until 2006, and that the IRB did not review research at a convened IRB meeting until Fall 2006. Two other individuals informed OHRP that they were never members of any BSC IRB. In addition, two of the four individuals informed OHRP that the individual identified as the Chairperson of the BSC IRB on the November 2004 IRB membership roster never served in this capacity. OHRP did not question the other two individuals about the person who was identified as the BSC IRB Chairperson on the November 2004 BSC IRB roster given that these two individuals informed OHRP that BSC did not have an IRB until 2006.

OHRP notes that the information provided to OHRP during the June 15, 2007 videoconference is in direct contradiction to the certifications of IRB approval for the above-referenced research and grant award that were submitted to HHS by BSC prior to Fall 2006. The information provided in BSC's August 23, 2006 and April 27, 2007 letters to OHRP, coupled with the lack of documentation evidencing that IRB review occurred prior to Fall 2006, also fails to substantiate BSC's certifications of IRB approval. In particular, OHRP notes the following:

(a) In the IRB certification sections of the 2005 and 2006 grant progress reports for the above-referenced grant, signed May 31, 2005 and May 25, 2006, BSC certified that the non-exempt human subjects research being conducted under the grant received full IRB review and approval in April 2004.[2]

(b) On June 16, 2006, an official at the National Institutes of Health (NIH) sent an e-mail to the principal investigator for the above-referenced grant requesting documentation of the date of the most recent BSC IRB approval for this grant. On June 20, 2006, apparently in response to this e-mail, BSC submitted to NIH via facsimile a document signed by you indicating that on June 19-20, 2006 the BSC IRB approved the Breast Cancer Study, one of the studies being conducted under the above-referenced grant. Finally, in its April 25, 2007 letter to OHRP, BCS stated the following regarding the documentation of the June 2006 IRB review of the Breast Cancer Study:

> "The review that occurred in June of 2006 at which time IRB members were not on campus and members were requested to approve the study without seeing any documentation by signing the forms.… However, this research was discussed by

[2] BSC stated in these progress report that the studies associated with grant 1R24 MD001107-01 underwent full board (IRB) review in April 2004. In a letter dated April 25, 2007, you clarified that the HIV Study (which was explained in the original grant application) was never implemented at BSC; instead, it was replaced by the Type 2 Diabetes Study after the HIV study investigator left BSC on May 14, 2004. Thus, the progress report statements regarding April 2004 full IRB review pertain to the Breast Cancer Study and the HIV Study; the only two studies in existence at the time of the alleged April 2004 IRB review.

the IRB Committee appointed in the fall 2006 semester and was approved by this group."

(c) In its March 20, 2007 letter, OHRP raised a concern regarding the failure of BSC to provide documentation substantiating that the BSC IRB approved the three HHS-supported research projects referenced above prior to initiation of the research projects as required under HHS regulations at 45 CFR 46.103(b) and 45 CFR 46.109(a) and conducted continuing review of these projects at least annually as required under HHS regulations at 45 CFR 46.109(e). In response, BSC in its April 25, 2007 letter provided the following explanation in reference to this concern: "Originally, notification of IRB approval for this study was given verbally to Dr. Anthony Woart by the IRB Chair at that time, Dr. Shekhar Pradham, who has since left the institution. There is no documentation regarding members of an IRB reviewing this study."

(d) BSC provided no minutes of IRB meetings for the studies that allegedly underwent review by the convened IRB, as are required to be maintained by BSC or its IRB under HHS regulations at 45 CFR 46.115(a)(2).

(e) BSC provided no documentation demonstrating that BSC IRB members were advised of research proposals approved under expedited review procedures as required by HHS regulations at 45 CFR 46.110(c), although in its August 23, 2006 letter, BSC stated that: "… our investigation revealed that although the full IRB members did not participate in the review, all research projects conducted at the BSC Minority Health Institute Center for Excellence were approved by the BSC Institutional Review Board prior to the initiation of the research projects and that the projects continued to be reviewed by the BSC IRB during the project period under review."

(f) BSC provided no evidence that the investigators were given written notification of IRB approval of the studies as required by HHS regulations at 45 CFR 46.109(d). In addition, BSC did not provide a date in which verbal approvals/re-approvals, which are noted in (2)(b) above, were communicated to the investigators.

(3) HHS regulations at 45 CFR 46.107(d) require that each IRB include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution. According to information provided by BSC in its April 25, 2007 letter and an interview with you during the June 15, 2007 videoconference, all members of the BSC IRB, constituted as of Fall 2006, are affiliated with BSC. Therefore, OHRP finds that the BSC IRB does not include at least one member who is not otherwise affiliated with BSC and who is not part of the immediate family of a person who is affiliated with BSC.

(4) HHS regulations at 45 CFR 46.107(a) provide, among other things, that the IRB shall be sufficiently qualified through the experience and expertise of its members to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects and shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. OHRP finds that the current BSC IRB Chairperson lacks a detailed understanding of the specific requirements of the HHS regulations for the protection of human subjects. For instance, during the June 15, 2007 videoconference the IRB Chairperson was unable to provide OHRP with the criteria that the BSC IRB considers when reviewing non-exempt human subjects research.

(5) OHRP reviewed the revised informed consent documents for the Type 2 Diabetes Study that were provided with BSC's April 25, 2007 letter. OHRP finds that the revised informed consent documents fail to include a statement that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled as required by HHS regulations at 45 CFR 46.116(a)(8).

(6) OHRP reviewed the informed consent documents for the Breast Cancer Study that were provided with BSC's April 25, 2007 letter. OHRP finds that the informed consent documents failed to include the following basic 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.

(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)(5): A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.

(e) 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.

(f) Section 46.116(a)(8): A statement that 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.

(7) Based on information provided by BSC in its August 23, 2006 and April 25, 2007 letters to OHRP, OHRP, in a letter dated March 20, 2007, made the following findings regarding the BSC IRB review of the above-referenced research and its written procedures. These findings were based on the belief that BSC had a duly constituted, functioning IRB prior to Fall 2006. OHRP has changed its view as a result of information provided to OHRP during the June 15, 2007 videoconference. See finding (2) above.

(a) OHRP found that that the BSC IRB lacked sufficient information, both at initial and continuing review, to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111.

(b) OHRP found that the BSC IRB failed to conduct substantive and meaningful continuing review of research, in specific, the Breast Cancer Study, at least once per year, as required by HHS regulations at 45 CFR 46.109(e).

(c) OHRP found no evidence that the BSC IRB made the findings required under HHS regulations at 45 CFR 46.404-407 when reviewing the Type 2 Diabetes Study, which involved children.

(d) OHRP found no documentation that the BSC IRB reviewed and approved protocol changes to a study, in specific the Breast Cancer Study, prior to initiation, as required by HHS regulations at 45 CFR 46.103(b)(4).

(e) OHRP found no evidence that the BSC IRB reviewed the HHS grant application referenced above prior to the initiation of research, as required by HHS regulations at 45 CFR 46.103(f).

(f) OHRP found no evidence that the BSC IRB maintained the documentation of its activities, as required by HHS regulations at 45 CFR 46.115(a).

(g) OHRP found that the Type 2 Diabetes Study informed consent document failed to include certain basic elements required by HHS regulations at 45 CFR 46.116(a).

(h) OHRP found exculpatory language in the Type 2 Diabetes Study informed consent documents in violation of HHS regulations at 45 CFR 46.116.

(i) OHRP found that an IRB member who had 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).

(j) OHRP found that BSC did not have the following written IRB procedures, as required by HHS regulations at 45 CFR 46.103(b)(4) and (5):

- Procedures the IRB will follow for conducting its initial review of research.
- Procedures the IRB will follow for conducting its continuing review of research.
- 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.
- 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 notes that in light of the new finding that BSC did not have a duly constituted, functioning IRB until Fall 2006 at the earliest (see finding (2) above), the deficiencies in BSC's system for protecting human subjects and extent of the non-compliance with the IRB review requirements under HHS regulations at 45 CFR part 46 with respect to the above-referenced research are actually more extensive and serious than was reflected in the findings made by OHRP in its March 20, 2007 letter.

OHRP acknowledges that BSC's April 25, 2007 letter described corrective actions being undertaken by BSC to address OHRP's March 20, 2007 findings. OHRP finds that, except for the corrective actions proposed in response to findings 7(d) and (i) above, the proposed corrective actions were inadequate. Furthermore, the proposed corrective actions do not address findings (1) to (6) above.

OHRP Action

In view of the above determinations and in order to ensure adequate protections for human subjects, OHRP hereby suspends the Bluefield State College Assurance (FWA-10457) in accordance with HHS regulations at 45 CFR 46.103(e), pending satisfactory completion of the required actions described below.

This suspension of FWA-10457, effective immediately, removes the Assurance required by HHS regulations at 45 CFR 46.103(a) for all U.S. federally supported research involving human subjects at Bluefield State College covered by the FWA.

As a result, all <u>U.S. federally supported</u> human subjects research projects to which the FWA applies must be suspended. For any project affected by this suspension, enrollment of new subjects must cease immediately except in extraordinary cases approved in advance by OHRP. OHRP would expect approval requests for such cases to be rare. Furthermore,

research activities involving previously enrolled subjects may continue only where it is in the best interests of such subjects. For each affected protocol this suspension must remain in effect until OHRP approval of the FWA is reinstated.

Required Actions Necessary for Reinstatement of FWA-10457:

(1) BSC must develop a satisfactory corrective action plan to address all deficiencies noted above.

(2) No later than July 16, 2007, BSC must provide a complete list of all U.S. federally supported research protocols that were suspended. Include the project title, principal investigator, IRB project number, and the Federal department or agency project number. BSC should identify those projects which BSC determines that research activities in previously enrolled subjects may continue because it is in the best interests of the individual subjects. Please describe the procedures used to make such determinations.

(3) BSC must provide a satisfactory response to the following additional questions and concerns regarding the human subject research protocols referenced above:

(a) [Redacted]

(b) [Redacted]

Guidance to Assist BSC in Developing an Adequate Corrective Action Plan

(1) OHRP notes that Section 8 of the new BSC IRB policy only addresses: (a) when a protocol must be submitted to the BSC IRB; (b) the documentation that must be submitted to the BSC IRB; and (c) how the documentation is triaged/distributed once received by the BSC IRB; Section 8 of the new IRB policy does not identify the information and criteria that must be reviewed and satisfied before the BSC IRB can approve/re-approve research. OHRP acknowledges that the new IRB application form attempts to collect some of the information that must be considered prior to approving research under HHS regulations at 45 CFR 46.111. OHRP notes, however, that the BSC IRB application form is insufficient in that it fails to solicit the following information: (a) how risks to subjects are minimized; (b) whether risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonable be expected to result; and (c) whether selection of subjects is equitable.

BSC's corrective action plan should include expansion of the IRB policies and procedures to include more details about the how the BSC IRB conducts initial and continuing review (see OHRP's Guidance on Written IRB Procedures available at http://www.hhs.gov/ohrp/humansubjects/guidance/irbgd107.htm). Furthermore, OHRP recommends that BSC develop a more robust IRB application form and an IRB reviewer checklist that takes into consideration all of the criteria outlined in HHS regulations at 45 CFR 46.111.

(2) BSC appears to misunderstand the purpose of the Individual Investigator Agreement (IIA). An IIA form outlines the responsibilities that a collaborating investigator at another institution has with an institution that holds an FWA and has agreed to allow the IRB designated under its FWA to review and approve research being conducted by that investigator; this form does not address the criteria that must be satisfied in order for an IRB to approve research under 45 CFR 46.111, nor does it address the documentation that an IRB is required to maintain under 45 CFR 46.115(a).

(3) BSC's corrective action plan should address 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. In particular, the corrective action plan should include expansion of the IRB policies and procedures to include more details about how the BSC IRB conducts continuing review. OHRP recommends a procedure detailing how the BSC IRB: (a) informs investigators of protocol expiration dates; (b) identifies protocols that are due for continuing review; (c) notifies investigators of upcoming review; and (d) processes studies for continuing review.

(4) BSC's corrective action plan should address the additional protections and considerations that must be taken into account by the BSC IRB when reviewing research involving children as research subjects (see 45 CFR part 46, subpart D).

(5) OHRP recommends that BSC's new IRB policy address how BSC will ensure that the BSC IRB approves informed consent information that contains the elements required under HHS regulations 45 CFR 46.116(a) and (b), unless a waiver or alteration of the requirements for informed consent is approved by the BSC IRB.

(6) BSC's corrective action plan should include expansion of the IRB policies and procedures to include the following:

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

(b) 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.

(c) 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; and (b) any serious or continuing noncompliance with 45 CFR part 46 or the requirements or determinations of the IRB.

OHRP encourages BSC to refer to OHRP's Guidance on Written IRB Procedures, available at http://www.hhs.gov/ohrp/humansubjects/guidance/irbgd107.htm, when drafting the procedures.

OHRP encourages BSC to develop its corrective action plan expeditiously and forward it to OHRP for review as soon as possible. OHRP is available to assist BSC in the development and implementation of the corrective action plan. Do not hesitate to contact me should you have any questions.

Sincerely,

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

cc: Dr. Tracey K. Anderson, Director of Institutional Research and Effectiveness, BSC
Dr. Anthony T. Woart, BSC
Dr. Lana Skirboll, OD, NIH
Dr. Sam Shekar, OER, NIH
Dr. Andrew C. von Eschenbach, Commissioner, FDA

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