DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852
Telephone: 240-453-8120
FAX: 240-453-6909
E-mail: Lisa.Rooney@hhs.gov

December 16, 2008

Ahmed C. Bawa, Ph.D.
DVC
University of KwaZulu-Natal
Nelson R. Mandela School of Medicine
Private Bag X54001
Durban, KwaZulu Natal 4013
SOUTH AFRICA

RE: Human Research Subject Protections Under Federalwide Assurance (FWA) – 678

Dear Dr. Bawa:

Thank you for your October 30, 2008 letter in response to our August 13, 2008 letter regarding our evaluation of your institution's system for protecting human research subjects.

A. In our August 13, 2008 letter we determined that the University of KwaZulu-Natal (UKN) failed to have the following written Institutional Review Board (IRB) procedures as required by Department of Health and Human Service (HHS) regulations at 45 CFR 46.103(a), 45 CFR 46.103(b)(4) and 46.103(b)(5):

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

Corrective Action: UKN provided us with a draft version of the Biomedical Research Ethics Committee (BREC), Terms of Reference (hereinafter referred to as Terms of Reference) and section 3.7 of the BREC Standard Operating Procedures (SOPs). These procedures, along with section 3.6 of the BREC SOPs, when finalized, will satisfactorily address our prior determination and will be appropriate under the terms of UKN's FWA.

Required Action: Please provide us with final versions of the BREC Terms of Reference and BREC SOPs.

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

Corrective Action: UKN provided us with a draft version of section 4.1 of the BREC SOPs. The procedures outlined in this section, when finalized, will satisfactorily address our prior determination and will be appropriate under the terms of UKN's FWA.

Required Action: Please provide us with final versions of the BREC SOPs.

(3) 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.

Corrective Action: UKN directed us to section 4.1 of the BREC SOPs for the procedures referenced above. We reviewed this section of the BREC SOPs and found that this section does not discuss such procedures; rather section 4.1 of the BREC SOPs discusses BREC/investigator responsibilities regarding recertification/continuing review of non-expedited studies. As a result, we determine that UKN does not currently have written IRB procedures that adequately describe the verification procedures noted above.

Required Action: Please provide us with the written procedures outlined above. We recommend that you refer to the Office for Human Research Protections' (OHRP's) Guidance on Written IRB Procedures, available at http://www.hhs.gov/ohrp/humansubjects/guidance/irbgd107.htm, when drafting the procedures.

(4) 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, are not initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

Corrective Action: UKN directed us to sections 7.1(g) and 17.5 of the BREC SOPs for the procedures referenced above. We reviewed these sections and found that these sections do not discuss such procedures. Instead, section 7.1(g) of the BREC SOPs discusses variations in informed consent procedures and section 17.5 discusses reports of serious adverse events, protocol deviations and violations. We did, however, review section 17.4 of the BREC SOPs which provides the following: "Any proposed amendment of an approved study must be submitted to the Committee for further approval using the current BREC amendment application form with supporting documents, … . BREC approval must be received prior to implementation of the modifications/changes." Please note that according to HHS regulations at 45 CFR 46.103(b)(4)(iii), prior IRB review and approval of proposed changes is not required when such changes are necessary to eliminate immediate hazards to the subject. The procedures outlined in this section, when finalized, will satisfactorily address our determination and will be appropriate under the terms of UKN's FWA.

Required Action: Please provide us with final versions of the BREC SOPs.

(5) 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.

UKN directed us to sections 17.5 and 23 of the BREC SOPs for the procedures referenced above. We reviewed these sections and found that these sections do not include all the incidents noted above. For example, section 17.5 is too limited in that it only discusses the reporting of serious adverse events, protocol deviations and violations to certain individuals/entities within a specified timeframe; this section does not address procedures for prompt reporting of unanticipated problems involving risks to subjects or others; serious or continuing noncompliance with 45 CFR part 46 or the requirements or determinations of the IRB or any suspension or termination of IRB approval. Moreover, while section 23 of the BREC SOPs discusses the need to report of certain incidents, it does not describe the procedures for the prompt reporting of such incidents. In addition, neither section 17.5 nor 23 of the BREC SOPs mentions the procedures for reporting any termination of IRB approval. Lastly, we note that while section 17.6 of the BREC SOPs discusses suspension or termination of approval of a study, this section does not require that such suspensions/terminations must be reported to appropriate institutional officials, any department or agency head, and OHRP. As a result, we determine that UKN does not currently have written IRB procedures that adequately describe the prompt reporting procedures noted above.

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

B. We make the following additional determinations:

(1) 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, for those studies in which investigators continue to conduct non-exempt human subject research activities beyond the expiration date of IRB approval. Based on the response provided by UKN, we determine that investigators continued to conduct non-exempt human subject research activities beyond the expiration date of IRB approval for protocols E248/05 and E264/05.

Corrective Action: We note that UKN has taken steps with the investigators of E248/05 and E264/05 to rectify this noncompliance. Moreover, we note that UKN has revised section 4.0 of the BREC SOPs regarding BREC recertification/continuing review procedures. Lastly, we note that UKN utilizes a BREC Application for Recertification which informs investigators of their responsibilities associated with applying for

continuing review. The actions satisfactorily address this determination and are appropriate under the terms of UKN's FWA.

(2) HHS regulations at 45 CFR 46.115(a)(2) require 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; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution. We determine that UKN did not maintain IRB minutes in accordance with 45 CFR 46.115(a)(2) for the May 2007 – May 2008 University of KwaZulu-Natal IRB meeting minute excerpts for HHS-supported research. This determination is based on the following response provided by UKN:

> "Our Standard Operating Procedures state that BREC meeting decisions are made primarily by consensus. Only if consensus is not reached is a vote undertaken and recorded. No votes were taken for the period in question as reflected in the minutes because decisions are primarily made by consensus. Attendance at meetings is recorded in detail on the opening section of our minutes – these administrative sections of the minutes were not sent to you in our submission of 1st May 2008. … We agree however that many of the minutes are silent with regard to the decision and action to be taken on protocols, and record only the description of the study and the queries raised. …"

Corrective Action: We acknowledge that since January 2008, the UKN BREC has tried to ensure that a clear decision is recorded after each protocol discussion. Moreover, we note that UKN has taken steps to adjust sections 3.5 – 3.7 of the BREC SOPs to ensure that minutes will include a clear decision as required by HHS regulations at 45 CFR 46.115(a)(2). We reviewed the referenced sections of the BREC SOPs and determine that these sections do not address the meeting minute requirements outlined in HHS regulations at 45 CFR 46.115(a)(2). However, we note that section 2.4 of the BREC SOPs does outline the meeting minute requirements as outlined in HHS regulations at 45 CFR 46.115(a)(2). Revised section 2.4 of the BREC SOPs satisfactorily addresses this determination and is appropriate under the terms of UKN's FWA.

(3) According to HHS regulations at 45 CFR 46.108(b) and 46.109, continuing review of previously approved research must be conducted by the IRB (at intervals appropriate to the degree of risk, but not less than once per year) at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas, except where expedited review is appropriate under HHS regulations at 45 CFR 46.110(b). We determine that the UKN IRB employed expedited review procedures to conduct continuing review and approve HHS funded research that involved minimal risk, but did not appear in the categories of research published in the Federal Register and/or HHS funded research that involved greater than minimal risk. This determination is based on the following response that was provided by UKN:

> "The BREC SOPs for this time required that all recertifications were reviewed by a BREC subcommittee. These are presented to full BREC meetings in the form of an Annexure to the minutes, and are raised for discussion in convened quorate BREC meetings. All members have access to the full documents if they wish to examine the recommended decision."[1]

Following this explanation, UKN provided us with a list of 3 HHS funded studies that underwent continuing review via an expedited review procedure even though the studies did not appear in the categories of research published in the Federal Register and/or involved greater than minimal risk.

Corrective Action: UKN amended section 4.1 and 4.2 of the BREC SOPs to prevent this situation from recurring in the future. This action satisfactorily addresses this determination and is appropriate under the terms of UKN's FWA.

(4) HHS regulations at 45 CFR 46.103(b)(4)(iii) require that an 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. HHS regulations at 45 CFR 46.108(b) require that such review of proposed protocol changes must be conducted by the IRB at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas, except where expedited review is appropriate for minor changes under HHS regulations at 45 CFR 46.110(b)(2). We determine that the UKN BREC employed expedited procedures to review changes that were more than minor. This determination is based on the following response that was provided by UKN:

> "The BREC SOPs for this time required that all amendments were initially reviewed by a BREC subcommittee, unless referred to a convened meeting through the Chair. These are tabled for ratification at convened quorate BREC meetings in the form of an Annexure to the agenda. All members have access to the full documents if they wish to examine the recommended decision."[2]

Following this explanation, UKN provided us with a list of 3 HHS funded studies that underwent amendment review via an expedited review procedure even though the study amendments involved more than minor changes.

Corrective Action: UKN amended section 17.4 of the BREC SOPs to comply with these regulatory requirements. This action satisfactorily addresses this determination and is appropriate under the terms of UKN's FWA.

---

[1] Notwithstanding this statement, we note that section 4.4 of the BREC SOPs that were in effect at the time of evaluation provided that "Sub-Committee decisions may be implemented from the date of the sub-Committee review. All sub-Committee decisions will be taken to the monthly Biomedical Research Ethics Committee meeting for ratification."
[2] Ibid.

(5) HHS regulations at 45 CFR 46.108(b) require that, except when an expedited review procedure is used, research be reviewed at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in a nonscientific area. We determine that the UKN IRB failed to satisfy the quorum requirements for its November and December 2007 IRB meetings. Thus, any actions taken at these meetings must be considered invalid. This determination is based on the following response provided by UKN: "Review of our records show that two of the convened meetings (Nov 2007 and Dec 2007) were not quorate, however, based on the prevailing BREC criteria (50% of membership plus one)."

Corrective Action: UKN amended section 2.4 of the BREC SOPs to comply with these regulatory requirements. This action satisfactorily addresses this determination and is appropriate under the terms of UKN's FWA. We recommend that UKN revise this section of the BREC SOPs to include the requirement that in order to satisfy quorum under HHS regulations at 45 CFR 46.108(b), a nonscientist must be present.

Required Action: Please ensure that the UKN IRB re-reviews all HHS-supported research that was reviewed during the November 2007 and December 2007, if not already done. Please notify us when the re-review has been completed.

C. Questions and Concerns Regarding the Biomedical Research Ethics Committee Standard Operating Procedures (BREC SOPs):

[Redacted]

D. Recommendations Regarding UKN's Human Subject Protection Program:

HHS regulations at 45 CFR 46.305-306 require specific findings on the part of the IRB for approval of research involving prisoners. In specific, HHS regulations at 45 CFR 46.306(a) require that biomedical or behavioral research conducted or supported by HHS may involve prisoners as subjects only if the institution responsible for the conduct of the research has certified to the HHS Secretary that the IRB has approved the research under HHS regulations at 46.305. It is our understanding that UKN will certify to the HHS Secretary that the UKN IRB approved study BF140/07 – an HHS Center for Disease Control supported protocol involving prisoners - under HHS regulations at 46.305 before the research begins. We recommend that UKN amend section 13 of the BREC SOPs to comply with 45 CFR 46.305-306 regulatory requirements.

Please provide us with responses to the above determinations, questions and concerns by January 23, 2009. Please do not hesitate to contact me if you should have any questions regarding this matter, or need assistance in developing your corrective action plan. 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.

OHRP appreciates your institution's continued commitment to the protection of human research subjects.

Sincerely,

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

cc: Dr. Jagidesa Moodley, Administrator, Biomedical Research Ethics, U KwaZulu-Natal
Dr. Andrew C. von Eschenbach, Commissioner, Food and Drug Administration (FDA)
Dr. Joanne R. Less, FDA
Dr. Sherry Mills, National Institutes of Health (NIH), Office of Extramural Research
Mr. Joe Ellis, NIH, Office of Extramural Research
Dr. Doug Wassenaar, Chair, UKN Biomedical Research Ethics Committee Chair