DEPARTMENT OF HEALTH & HUMAN SERVICES
Office of the Secretary
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SOUTH AFRICA

RE: Human Research Subject Protections Under Federalwide Assurance – 678

Dear Dr. Bawa:

Thank you for your January 17, 2008 and May 29, 2008 reports in response to our December 6, 2007 and May 1, 2008 letters regarding our evaluation of your institution's system for protecting human research subjects. Based on the information submitted, we make the following determinations and raise the following questions and concerns regarding your institution's system for protecting human subjects:

A. <u>Determinations regarding your institution's system for protecting human subjects:</u>

(1) We reviewed the University of KwaZulu-Natal Biomedical Research Ethics Committee (hereinafter referred to as the University of KwaZulu-Natal institutional review board (IRB)) policies and procedures that were included with your January 17, 2008 report and determine that the University of KwaZulu-Natal fails to have the following written 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):

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

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

(c) 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.

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

(e) 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.

Required Action: Please provide OHRP 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. Questions and concerns regarding your institution's system for protecting human subjects:

(1) [Redacted]

[Redacted]

(2) [Redacted]

(3) [Redacted]

[Redacted]

(4) [Redacted]

(5) [Redacted]

(6) [Redacted]

(7) [Redacted]

(8) [Redacted]

[Redacted]

[Redacted]

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

[Redacted]

D. <u>Recommendations Regarding University of KwaZulu-Natal's human subject protection program:</u>

We recommend that you modify item (2) of the Biomedical Research Ethics Committee Terms of Reference to reflect that whenever the University of KwaZulu-Natal becomes engaged in non-exempt human subjects research that is conducted or supported by HHS, the University and any IRB designated under the University's Federalwide Assurance (FWA) must comply with the HHS protection of human subjects regulations at 45 CFR

part 46. We also recommend that you modify section 2.5 of the BREC SOPs to reflect that the University of KwaZulu-Natal and the Biomedical Research Ethics Committee must comply with HHS regulations at 45 CFR part 46 whenever the University becomes engaged in non-exempt human subjects research that is conducted or supported by HHS.

E. <u>Recommendations Regarding the BREC SOPs:</u>

(1) Section 2.4. We note that this section states that "Decisions will be determined by consensus (general agreement). Where general agreement does not exist, consensus will be undermined and the decision will be arrived at by vote." Please note that whenever the University of KwaZulu-Natal becomes engaged in non-exempt human subjects research that is conducted or supported by HHS, the University and any IRB designated under the University's Federalwide Assurance (FWA) must comply with HHS regulations at 45 CFR part 46, including 45 CFR 46.115(a)(2) which requires that minutes of IRB meetings be in sufficient detail, among other things, actions taken by the IRB and the vote on these actions including the number of members voting for, against, and abstaining. Thus, we recommend that you revise this section to include the regulatory requirements noted above.

(2) Section 6.0. We recommend that you revise this section to include all the criteria that must be satisfied in order for an IRB to approve non-exempt human subjects research that is conducted or supported by HHS. HHS regulations at 45 CFR 46.111(a) delineate that the following criteria must be satisfied in order for an IRB to approve non-exempt human subjects research that is conducted or supported by HHS:

(a) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
(b) 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. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
(c) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.
(d) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §46.116.
(e) Informed consent will be appropriately documented, in accordance with, and to the extent required by §46.117.

(f) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
(g) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

In addition, HHS regulations at 45 CFR 46.111(b) provide that when some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

(3) Section 7.0. We recommend that you revise this section to state that the following specific elements are required for informed consent for non-exempt human subjects research that is conducted or supported by HHS, unless the elements have been waived or altered by the IRB in accordance with HHS regulations at 45 CFR 46.116(d):

(a) Section 46.116(a)(1): (i) A statement that the study involves research; (ii) an explanation of the purposes of the research (i.e., [summary of purpose]); (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 (i.e., [procedures not described]).
(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.g., [alternatives which should be described]).
(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.

We also recommend that you review your sample informed consent documents to ensure that the documents contain all applicable informed consent elements in accordance with HHS regulations at 45 CFR 46.116.

Please provide us with responses to the above determination, questions and concerns by September 19, 2008. 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