DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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Zerababel M. Nyiira, Ph.D.
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Uganda National Council of
Science and Technology
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Kampala, Uganda

Nelson K. Sewankambo, M.D.
Uganda National Council of
Science and Technology
Makerere Medical School
P.O. Box 7072
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RE: Human Research Subject Protections Under Federalwide Assurance (FWA) 00001293, Single Project Assurances (SPA) S-6233 and S-6234, and Cooperative Project Assurances (CPA) T-5124 and T-5125

Research Project: **A Phase III Efficacy Trial of Oral AZT vs. Oral Nevirapine in HIV-1 Infected Pregnant Ugandan Women (HIVNET 012)**
Principal Investigator: Professor Francis Mmiro

Dear Dr. Nyiira and Dr. Sewankambo:

The Office for Human Research Protections (OHRP) has reviewed your reports dated April 5, 2002 and April 12, 2002 regarding allegations of serious noncompliance with Department of Health and

Human Services (HHS) regulations for the protection of human research subjects (45 CFR Part 46) at Makerere University (MU) and Mulago Hospital (MH).
OHRP notes the following:

(1) The Uganda National Council for Science and Technology (UNCST) currently operates under a Federalwide assurance (FWA) and has agreed to follow the Council for International Organizations of Medical Sciences (CIOMS) guidelines in conducting review of protocols by its Institutional Review Board (IRB), the National AIDS Research Committee (ARC).

(2) Prior to October 5, 2001, HHS-supported research conducted by the UNCST fell under single project assurances (SPA) and cooperative project assurances (CPA) which required MU to follow the HHS regulations for the protection of human subjects.

(3) The SPAs for the above-referenced research state, "Makerere University, hereinafter known as the 'institution', hereby gives assurance that it will comply with the Department of Health and Human Services (DHHS) regulations for the protection of human subjects (45 CFR 46) as specified below."

Based upon the review of your reports, OHRP makes the following determinations regarding the above-referenced research:

(1) HHS regulations at 45 CFR 46.109(e) require that an IRB shall conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year. OHRP notes that your April 12, 2002 report stated the following:

(a) "Annual progress reports were not submitted regularly by the investigators to the ARC for review and approval."

(b) "ARC or UNCST has not had a mechanism for tracking annual review dates for projects because of its very limited resources. As a consequence the committee has not had a procedure for notification of annual review dates and follow-up of investigators who may default from timely submission of annual progress reports."

As a result, OHRP finds that the ARC failed to conduct continuing review of the above-referenced research as required by HHS regulations at 45 CFR 46.109(e).

Corrective Action: OHRP notes the commitment of the UNCST to obtain funding to support the ARC and its operations, including the tracking of protocols for continuing review. Additionally, OHRP acknowledges that the ARC has agreed to hire new staff to oversee regulatory compliance activities.

(2) HHS regulations at 45 CFR 46.103(b)(4)(iii) require that changes in IRB-approved research may not be initiated without IRB review and approval except when necessary to

eliminate apparent immediate hazards to the subject. OHRP notes the following:

(a) The IRB-approved protocol stated the following:

(i) "An adverse event (AE) is defined as any health-related reaction, effect, toxicity or abnormal laboratory result that a participant experiences during the course of a study irrespective of relationship to the study treatment."

(ii) "The severity of adverse experiences will be graded using standardized study toxicity tables, to be included in the Manual of Study Operations."

(iii) "A serious adverse event is defined as any experience that is fatal or life-threatening, permanently disabling, requires in-patient hospitalization, is a congenital anomaly, cancer or overdose or is otherwise judged to be serious by the on-site clinician."

(iv) "Criteria for toxicity are based upon the DAIDS Toxicity Tables for neonates, children and adults."

(b) The Adverse Event Reporting Criteria Procedures supplied with your April 12, 2002 report stated the following:

(i) With respect to life threatening illnesses, the criteria stated "[d]ue to the nature of the underlying health and nutritional status of the study population, some illnesses or laboratory abnormalities that under normal circumstances may be life threatening (Grade 3-4 on toxicity tables) were not considered as such."

(ii) With respect to illnesses judged to be serious by the on-site clinician, the criteria stated:

a. "The main determination of seriousness was whether the illness was serious enough to require hospitalization."

b. "Given the very high rates of illness in this population, some differentiation was needed in order to identify children with the most severe illnesses. Children with illnesses that could be managed at home were not considered serious. High grade laboratory toxicities alone were not considered serious unless they were accompanied by clinical symptoms of the same magnitude."

(iii) "Clinical events were generally graded according to the scale outlined below:

a. Illnesses that were thought to be immediately life threatening were considered grade 4.

b. The illnesses that led to most hospitalizations were considered grade 3 unless they were clearly admitted for an illness less severe than other children admitted with the same diagnosis.

c. Illnesses with significant signs and symptoms requiring medical management but not requiring hospitalization were considered grade 2.

d. Illnesses with minimal signs and symptoms that could be managed easily with no therapy or with minimal routine oral or topical therapy (antibiotics, analgesics, chloroquine, etc.) were considered grade 1."

OHRP finds no documentation that the investigators obtained IRB approval for the changes in reporting criteria and toxicity severity grading, in contravention of HHS regulations at 45 CFR 46.103(b)(4)(iii). Furthermore, OHRP is concerned that the alteration of reporting criteria may have represented a failure to minimize risk to the subjects.

In addition, OHRP notes that your April 12, 2002 report indicated that there were other instances where the investigators for the above-referenced research failed to follow the IRB-approved study protocol.

Based on its review of your reports, OHRP makes the following additional determinations regarding the system for the protection of human subjects overseen by the ARC:

(3) HHS regulations at 45 CFR 46.111 require that, in order to approve research covered by the regulations, the IRB shall determine that certain criteria are satisfied. OHRP finds that for some research protocols, the IRB appeared to fail to make the determinations required for approval under HHS regulations at 45 CFR 46.111 or lacked sufficient information to make these determinations. In particular, OHRP notes the following:

(a) Regarding the protocol entitled "Dose-modified oral combination chemotherapy in patients with AIDS-related non-Hodgkins lymphoma i[n] the United States and Africa," the minutes of the November 25, 1999 IRB meeting stated, "There are ethical issues that are outstanding." OHRP is concerned that despite the cited outstanding ethical issues, the IRB approved the study.

(b) Regarding the protocol entitled "Human papilloma infections in women attending the national sexual transmitted diseases (STD) referral center in Uganda: Prevalence, genotypes and relationships to HIV infection, other STDs and cervical intraepithelial

lesion," the minutes of the May 24, 2001 IRB meeting stated, "A very important study but Questionnaire is not attached." OHRP is concerned that the IRB approved the study without having all the necessary information on which to base its approval.

(c) Regarding the study entitled "Hormonal contraception, herpes simplex virus-2 and HIV infection. A sub-study of HIVNET 021," the minutes of the July 23, 2001 IRB meeting stated, "No reviewers comments yet. If no comments from reviewers for another 2 weeks then the Secretary and Chairman to review and [m]ake a decision for the committee." OHRP is concerned that the Secretary and Chairman of the IRB may have approved the protocol (which does not appear to be eligible for expedited review) without the review and approval of the convened IRB.

(4) 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 and 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. Additionally, where the convened IRB specifies conditions for approval of a protocol that are to be verified as being satisfied by the IRB Chair or another IRB member designated by the Chair, continuing review must occur no more than one year after the date the protocol was reviewed by the convened IRB, not on the anniversary of the date the IRB Chair or his or her designee verifies that IRB-specified conditions for approval have been satisfied.

OHRP found numerous instances in which the ARC failed to conduct continuing review of research at least once per year. If an IRB does not re-approve the research by the specified expiration date, subject accrual should be suspended pending re-approval of the research by the IRB. Enrollment of new subjects ordinarily cannot occur after the expiration of IRB approval. Continuation of research interventions or interactions in already-enrolled subjects should continue only when the IRB finds that it is in the best interests of individual subjects to do so.

(5) HHS regulations at 45 CFR 46.115(a) require that the institution prepare and maintain adequate documentation of IRB activities. OHRP finds that the records of the ARC fail to meet this requirement. In many cases, the contents of IRB files did not contain copies of (i) all versions of the protocols or informed consent documents that were reviewed; (ii) progress reports from investigators; and (iii) reports of injuries or unanticipated problems involving risks to subjects. In numerous instances among the IRB files examined by OHRP, it was difficult to reconstruct a complete history of all IRB actions related to the review and approval of the protocol. In some instances, OHRP could not determine what the IRB actually approved.

Specifically, OHRP notes the following:

(a) Your April 5, 2002 report stated "[o]n the failure of the IRB to maintain adequate

documentation of IRB activities as required by HHS regulations at 45 CFR 46.115, and incompleteness of the IRB records on HIVNET 012 study, the Council accepts this observation and wishes to indicate that Uganda, like many other developing countries, generally lacks adequate capacity to ensure proper documentation, storage and retrieval of information."

(b) The protocol file for the study entitled "Impact of Tuberculosis on HIV in Kampala, Uganda: Phase II Clinical Trial of Immunoadjuvant Therapy for HIV-associated Tuberculosis with Prednisolone" contains copies of protocols from as early as November 17, 1998 (version 2.70) but does not contain any documentation of the initial approval of the research.

(c) The protocol file for the study entitled "Pilot Immunology Study to Assess Ex vivo Regulation of Host Cell-Mediated and Humoral Immune Response During Short Course Anti-TB Treatment of HIV-non-infected Adults with Initial Episodes of Smear Positive Pulmonary Tuberculosis (TBRU #4)" contains no documentation for the approvals of Version 1.0, dated May 15, 1995, or for Version 1.2, dated November 21, 1997.

(d) The protocol file for the study entitled "The Role of M. Africanum in Human Tuberculosis in Uganda" indicated that the study was closed, but the file contained no documentation regarding the closing of the study.

(6) HHS regulations at 45 CFR 46.109(d) require that an IRB shall notify investigators and the institution in writing of its decision to approve or disapprove a proposed research activity, or of modifications required to secure IRB approval of the research activity. OHRP finds little evidence that the ARC provides investigators with written comments which must be addressed before the research may be approved. For example, OHRP notes that on February 1, 2001 the ARC received an amendment for the study entitled A Phase I Study of the Virology, immunology, and Safety of TNFR:FC (Embrel, Immunex) in HIV-Infected Adults with Tuberculosis. A May 16, 2001 memo from the ARC to the principal investigator indicated that the concerns of the ARC had been addressed but the file contains no documentation of what the concerns were or any copy of a written response from the investigator.

(7) HHS regulations at 45 CFR 46.108(b) require that, except when an expedited review procedure is used, the IRB review proposed research 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. OHRP finds that the ARC failed to meet this requirement for the September 20, 2001 meeting. Thus, any actions taken at these meeting must be considered invalid. In addition, minutes of the ARC's February 12, 1999 meeting stated that four members were present and stated "[t]he rest of the members" were absent without apology. Based upon the membership listed for the ARC's April 15, 1999 meeting, an IRB

meeting held with four members present does not appear to meet the requirements of 45 CFR 46.108(b). OHRP emphasizes that should the quorum fail during a meeting (e.g., those with conflicts being excused, early departures, absence of a nonscientist member), the IRB may not take further actions or votes unless the quorum can be restored.

(8) 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. OHRP finds that the ARC's minutes often failed to meet these requirements. For example, OHRP notes that (i) no list of attendees was provided with the minutes of the November 30, 2001 IRB meeting; (ii) no votes on actions taken by the IRB are listed in the minutes; and (iii) in many cases there is no description of the comments of the IRB or the required changes necessary to secure approval.

(9) HHS regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5) require that institutions have written IRB procedures that adequately describe the following activities:

(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.

OHRP finds that the written procedures submitted with your reports failed to meet these requirements.

Required Action 1: The ARC, in conjunction with all of its investigators and clinical practitioners, as well as relevant administrators, must audit and identify all ongoing HHS-supported research projects involving human subjects that are not exempt under HHS regulations at 45 CFR 46.101(b) and confirm that all such research underwent appropriate initial or continuing review by the ARC within the past year and satisfied the criteria required for approval under HHS regulations at 45 CFR 46.111. The ARC must suspend immediately any nonexempt research involving human subjects that has not been reviewed and approved by the ARC. By August 30, 2002, please provide OHRP with a report on the results of this audit and a list of any research activities that have been suspended as a result of this audit

Required Action 2: By August 30, 2002, the ARC must submit to OHRP a satisfactory corrective action plan that addresses findings (2) - (9) above. The corrective action plan should include revised IRB policies and procedures addressing each of the issues raised in findings (2) - (9) and copies of minutes of IRB meetings which document changes which have been made with respect to the ARC's documentation of discussions and actions of the IRB.

Required Action 3: By August 30, 2002, the ARC must submit to OHRP a detailed plan for ensuring that all research investigators, all IRB members, and all IRB staff are appropriately educated, on an ongoing basis, about ethical principles and regulatory requirements for the protection of human subjects.

Please note that failure to provide a satisfactory response to the above required actions may result in suspension of the UNCST FWA.

OHRP has the following additional concerns regarding the system for the protection of human subjects overseen by the ARC:

(10) [redacted].

(11) [redacted].

Please include your response to these additional concerns with your report due to OHRP no later than August 30, 2002.

Sincerely,

Patrick J. McNeilly, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Edward K. Mbiode, IRB Chair
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