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April 21, 2008

Mary B. Burnside
University of California at Berkeley
Vice Chancellor for Research
Office of the Vice Chancellor for Research
119 California Hall
Berkeley, California 94720-1500

RE: Human Research Subject Protections Under Federalwide Assurance – 6252

Research Project:	Follow-up of the Multimodal Treatment Study of Children with ADHD: MTA Study
UCB Protocol Number:	2004-3-6
Sponsor:	National Institutes of Health
Research Project:	Labor Supply and Compensating Differentials for Commercial Sex Workers in Kenya
UCB Protocol Number:	2005-5-2
Sponsor:	National Institutes of Health
Research Project:	Prospective Hospital-Based Study of Dengue Classification and Case Management in Nicaragua
UCB Protocol Number:	2005-5-35
Sponsor:	National Institutes of Health

Dear Ms. Burnside:

Thank you for your August 31, 2007, October 17, 2007 and February 20, 2008 letters in response to our June 29, 2007 and October 10, 2007 letters regarding research conducted under the above-referenced Federalwide Assurance (FWA) and, in specific, research conducted in the above-referenced research projects.

A. Previous Determinations and Corrective Actions

In our June 29, 2007 letter, we made the following determinations:

(1) We determined that the University of California, Berkeley (UCB) did not have written institutional review board (IRB) procedures that adequately described numerous activities as outlined in Department of Health and Human Subjects (HHS) regulations at 45 CFR 46.103(a), 45 CFR 46.103(b)(4) and 46.103(b)(5).

Corrective Action: UCB has provided us with revised written UCB IRB policies and procedures which adequately address this determination.

(2) We determined that the UCB IRB, the Committee for Protection of Human Subjects (CPHS), did not obtain sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. In specific, we determined that CPHS did not review survey instruments prior to approving/re-approving research involving the use of such instruments.

Corrective Action: We note that in September 2005 the CPHS Application Form was revised to include a checklist to assist investigators in submitting more complete applications; including the submission of "Data Collection Instruments (e.g., surveys, interview guides)." We further note that the CPHS Protocol Narrative Form (dated October 2007) was revised to, among other things, instruct investigators to submit for IRB review copies of all data collection instruments, both standard and non-standard, that will be used for the study. Lastly, we acknowledge that at continuing review, CPHS will be requiring investigators to submit any data collection instruments that appear to be missing from study-specific CPHS records.

(3) We determined that CPHS did not make required findings under 45 CFR part 46, subpart D (Additional Protections for Children Involved as Subjects in Research) when reviewing research involving children.

Corrective Action: We acknowledge that since 2005 the UCB Office for Protection of Human Subjects (OPHS), the administrative office of CPHS, has developed checklists and worksheets for staff and CPHS members to improve documentation of required findings/determinations. One of the worksheets that is now used - OPHS Worksheet Permissible Research With Children - includes the list of permissible categories of research involving children. Moreover, we acknowledge that UCB reviewed all currently active research studies involving children and receiving HHS support and determined that all of the currently active studies have the appropriate subpart D findings documented.

(4) We determined that CPHS inappropriately applied expedited review category (2) to the research study *Prospective Hospital Based Study of Dengue Classification and Case Management in Nicaragua* (Study 2005-5-35).

Corrective Action: We acknowledge that OPHS staff and the CPHS Chair/designee have been reminded to ensure that study procedures are clearly laid out in the protocol

and consent materials and to check that study procedures correspond to the expedited categories referenced/selected. In addition, we note that the OPHS Staff Review Sheets for new and continuing expedited review applications now: (1) include a list of the expedited categories in their entirety; and (2) request the IRB Chair/designee to confirm that research falls within one of the permissible expedited review categories.

(5) We determined that informed consent documents and parental permission forms that were reviewed and approved by CPHS did not include all of the elements outlined in HHS regulations at 45 CFR 46.116.

Corrective Action: We note that OPHS staff, the CPHS Chair/Designee and CPHS primary and secondary reviewers are asked to use an informed consent checklist that contains the basic and additional elements of informed consent as set forth at 45 CFR 46.116(a) and (b).

(6) We determined that the CPHS study files for two separate protocols did not include information as required by 45 CFR 46.115(a)(1). As a result, it was difficult to reconstruct a complete history of all IRB actions related to these protocols.

Corrective Action: We note that OPHS staff has been given a refresher course concerning what information must be in included in IRB files and have been reminded of the importance of maintaining complete and accurate records of IRB activities. Furthermore, we acknowledge that UCB P&Ps: RR 401- RR 404; 408, and 411 provide that an OPHS staff reviewer is responsible for ensuring that all of the appropriate documents are submitted and presented in an organized manner to the IRB or designated IRB member for review.

(7) We determined that CPHS continuing review of *Follow-up of the Multimodal Treatment Study of Children with ADHD: MTA Study* (Study 2004-3-6) was not substantive and meaningful.

Corrective Action: We acknowledge that UCB has authored written IRB procedure: RR 403 – Continuing Review. We further acknowledge that effective September 4, 2007, OPHS implemented the new Staff Review Sheets for Expedited Continuations/Renewals and the Staff Summary Templates for Full Committee Continuations/Renewals.

(8) We determined that CPHS approved research contingent upon substantive modifications or clarifications that are directly relevant to the determinations required by the IRB under HHS regulations at 45 CFR 46.111, without requiring additional review by the convened IRB.

Corrective Action: We note that UCB has educated the CPHS Chair/Vice Chair and CPHS II Chair about this determination via various mechanisms. We also note that all CPHS members and alternates will be educated about this issue. Lastly, we note that UCB has revised various forms to ensure that all applicable 45 CFR 46.111 criteria are collected/considered/satisfied prior to granting IRB approval of research.

(9) We determined that UCB provided no evidence demonstrating that CPHS determined and documented that the four criteria outlined at HHS regulations at 45 CFR 46.116(d) were satisfied prior to approving waiver or alteration of some or all of the required elements of informed consent under study *Sex Work as a Response to Risk in Kenya* (Study 2005-5-2).

Corrective Action: We acknowledge that OPHS has developed checklists and worksheets for OPHS staff and CPHS members that include the criteria outlined at HHS regulations 45 CFR 46.116(c) and (d). We note that CPHS will ensure that these criteria are satisfied and documented prior to approving waiver or alteration of some or all of the required elements of informed consent.

B. Additional Determinations and Corrective Actions

At this time, we make the following additional determinations:

(1) We acknowledge the additional steps that UCB took to investigate the allegation regarding the failure of CPHS to make required findings under 45 CFR part 46, subpart C and 45 CFR 46.409 when reviewing Study 2004-3-6; research allegedly involving both prisoners and wards of the state. In specific, we appreciate the investigator's response regarding the enrolled subject population, which consisted of non-prisoners and non-wards.

Based on the information provided, we determine that the allegation of noncompliance is unproven. No evidence was presented to us indicating that prisoners and/or wards were enrolled into the study.

(2) We determine that CPHS did not conduct continuing review of research at least once per year as required by HHS regulations at 45 CFR 46.109(e) and that investigators continued to conduct research activities beyond the expiration date of IRB approval. We note that the UCB investigation revealed that 91 of 138 listed HHS funded active protocols had lapses in continuing review. Moreover, we note that UCB investigation found instances where investigators had not stopped their research activities upon the expiration date of IRB approval. The protocols that experienced such lapses consisted of research involving no more than minimal risk as well as research involving greater than minimal risk. We note that the lapses ranged in time from a few days to over several months.

Corrective Action: We acknowledge that UCB is taking/has taken the following steps to remedy the determinations noted above until a web-based online protocol submission and review management system is implemented:

(a) A specific "team" of three OPHS staff will be responsible for ensuring that all non-exempt protocols are reviewed and re-approved prior to expiration.

(b) A designated staff member will monitor, on a weekly basis, continuing review applications where a response to CPHS/OPHS is pending, i.e., where CPHS/OPHS is waiting on a response or clarification from an investigator before the application can go forward for review.
(c) Pre-reviews by staff for expedited continuing review will now be split between three rather than two individuals.
(d) Two new administrative analyst positions were added to the OPHS staff. These individuals will have responsibility for logins, the continuation/renewal reminder system, follow-up on pending studies and administrative closures.
(e) Increased outreach to investigators and the posting of new and revised policies and procedures are facilitating investigators' understanding and compliance.

(3) We determine that the CPHS did not notify investigators in writing of its decision to withdraw IRB approval for the addition of a funding source for study 2005-5-35 as required by HHS regulations at 45 CFR 46.109(d).

Corrective Action: We acknowledge that such written notification is stated as a requirement in written IRB procedure RR 407 – Categories of Action.

(4) HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the IRB **review** (emphasis added) 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. We determine that the CPHS did not **review** a new supplementary survey associated with the study *Sex Work as a Response to Risk in Kenya* (Study 2005-5-2) prior to approving the new supplementary survey as required by HHS regulations at 45 CFR 46.103(b)(4)(iii). This determination is based on the fact that UCB could not locate any documentation regarding the revised supplemental questionnaire in the study file, and UCB's resulting conclusion that "it does appear that the Chair approved it without having seen the document."

Corrective Action: We acknowledge UCB's statement that the CPHS Chair, designated reviewers, and committee members will be reminded that all relevant instruments will be reviewed before approval is issued. Moreover, we note that UCB written IRB procedure: RR 404 – Amendment (Revision) Review (last revised August 31, 2007) helps ensure that the IRB reviews proposed modifications prior to approving such modifications.

(5) We determine that a person unaffiliated with the IRB has been approving non-exempt human subject research in violation of HHS regulations at 45 CFR 46.103(b), 45 CFR 46.109(a) and 45 CFR 46.110(b) and/or that certain protocol changes were implemented without prior IRB review and approval in violation of HHS regulations at 45 CFR 46.103(b)(4)(iii). This determination is based on the following response that was provided by UCB:

> "In summary, a total of 135 expedited review actions occurred; in 56 of those actions, UCB does not have documentation that an IRB member

reviewed and approved the protocol or amendment; and out of the 135 protocols, 53 are currently open and active. All of the currently open and active protocols that did not previously have clear documentation of IRB member review have since had continuing review in which approval by an IRB member is clearly documented. UCB notes that 29 of the undocumented expedited actions involved amendments or modifications to a protocol."

Corrective Action: We note that UCB has drafted written IRB procedure RR- 402 and 404. These procedures are designed to ensure that a CPHS IRB member (vs. an OPHS staff person) reviews and approves all non-exempt human subjects research covered by the UCB FWA as required by HHS regulations at 45 CFR 46.103(b) and 46.109(a) and/or that the CPHS approves protocol changes prior to implementation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects as required by HHS regulations at 45 CFR 46.103(b)(4)(iii).

(6) We determine that UCB IRB members were not advised of a minor change in a research protocol approved under an expedited review procedure as required by HHS regulations at 45 CFR 46.110(c). This determination is based on the following statement made by UCB: "We could find no documentation indicating that the expedited approval of the minor amendment per the September 15, 2003 memorandum was reported to the IRB members. It could not be found in any reports of expedited actions."

Corrective Action: We acknowledge that UCB P&P: RR 402 –Expedited Review (dated August 31, 2007) helps ensure that IRB members are advised of minor changes in research protocols approved under an expedited review procedure as required by HHS regulations at 45 CFR 46.110(c).

C. Additional Guidance

At this time, we provide the following guidance in reference to the UCB Policies and Procedures submitted to us on August 31, 2007:

(1) GA 104 – IRB Member Conflict of Interest – We believe that the conflict of interest definition provided in this procedure is too limited. As you are aware, HHS regulations at 45 CFR 46.107(e) stipulate that no IRB member may participate in the IRB initial or continuing review of a project in which the member has a conflicting interest, except to provide information requested by the IRB. Please note that we have previously held that IRB members who were involved in research as research coordinators, protocol consultants and/or advisory committee members were considered to have a conflicting interest which should have prevented such IRB members from participating in the IRB initial or continuing review of the projects in which they were involved. As a result, we recommend that you expand the definition of conflict of interest noted in this procedure.

(2) GA 105 – Signatory Authority – We note that section 1.3 of this written IRB procedure does not appear to cover approval of modification requests. We suggest that this written IRB procedure be revised to cover approval of such requests.

(3) RR 407 – Categories of Action – We note that this policy (a) outlines the types of actions that may result from IRB review of research submitted for initial or continuing review and; (b) provides that the IRB will notify investigators in writing of such actions. We also note that RR 602 – Intrainstitutional Communication (last revised August 27, 2007) does not provide that the IRB will notify investigators in writing of its decision to approve or disapprove the proposed research activity as required by HHS regulations at 45 CFR 46.109(d). Given this discrepancy, we recommend that UCB modify written IRB procedure RR 602 to be consistent with language found in written IRB procedure RR 407, i.e., include language stating that the IRB will notify investigators in writing of its decision to approve/grant conditional approval/defer or disapprove the proposed research activity .

(4) SC 502 – Prisoners as a Vulnerable Population – We note that section 1.1.2 of this written IRB procedure references a minimal risk definition found in RR 401. We note, however, that RR 401 does not include a definition of minimal risk. We recommend that written IRB procedure RR 401 be revised to include a definition of minimal risk.

(5) CPHS Application Cover Sheet, Part VIII: Investigator Assurance - We note that this section of the form does not ask the investigator to notify CPHS of serious or continuing noncompliance with 45 CFR part 46 or the requirements or determinations of the IRB. We recommend that the application cover sheet be revised to instruct the investigator to notify CPHS of such incidents.

(6) Staff Review – Expedited Amendment(s). It is not clear why the 7 expedited review categories are listed on this form when the form is intended to assist OPHS staff regarding proposed changes in previously approved research. We recommend omitting the list of expedited review categories from this form.

(7) Report of Unanticipated Problems or Serious Adverse Events Form. We note that this form is targeted to address Unanticipated Problems or Serious Adverse Events as such problems/events relate to physical risks. This form does not appear to take into account non-physical harms, e.g., breach of confidentiality, dignitary risks, etc. We recommend revising this form to include such other types of risks.

We acknowledge all of the remaining UCB responses that are not specifically addressed above.

We have determined that the corrective actions noted above adequately address our determinations and are appropriate under the UCB FWA. As a result, there should be no need of further involvement of our office in this matter. We anticipate conducting a site visit at your institution within the next 12-24 months.

We appreciate your institution's continued commitment to the protection of human research subjects. Please contact me if you should have any questions regarding this matter.

Sincerely,

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

cc: Dr. Rebecca D. Armstrong, HPA, UCB
Dr. Malcolm Potts, IRB Chairperson, UCB
Dr. Chris Ansell, IRB Chairperson, UCB
Dr. Sherry Mills, Office of Extramural Research, National Institutes of Health
Mr. Joe Ellis, OER, NIH