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

June 29, 2007

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
UC Berkeley Protocol Number:	2004-3-6
Sponsor:	National Institutes of Health
Research Project:	Labor Supply and Compensating Differentials for Commercial Sex Workers in Kenya
UC Berkeley Protocol Number:	2005-5-2
Sponsor:	National Institutes of Health
Research Project:	Prospective Hospital-Based Study of Dengue Classification and Case Management in Nicaragua
UC Berkeley Protocol Number:	2005-5-35
Sponsor:	National Institutes of Health

Dear Ms. Burnside:

The Office for Human Research Protections (OHRP) has reviewed University of California at Berkeley's (UC Berkeley's) September 20, 2006, March 19, 2007 and March 28, 2007 letters in response to OHRP's August 7, 2006 and March 9, 2007 letters regarding research conducted under the above-referenced Federalwide Assurance (FWA) and, in specific, research conducted under the above-referenced research projects.

OHRP acknowledges UC Berkeley's statement that "we do not specify in our federal wide assurance that we will apply 45 CFR 46, or its subparts, to research that is funded by non-federal monies." OHRP notes, however, that UC Berkeley voluntarily extended its Multiple Project Assurance (MPA)/FWA to all research, regardless of funding source, until July 2004; at which time UC Berkeley decided to limit the applicability of its FWA to research conducted or supported by the Department of Health and Human Services (HHS) or by any other federal department or agency that has adopted the Federal Policy for the Protection of Human Subjects, known as the Common Rule. Given these facts, OHRP has jurisdiction over all institutional review board (IRB) activities relating to non-exempt human subject research that occurred prior to July 2004, regardless of funding source. In addition, OHRP has jurisdiction over all IRB activities relating to non-exempt human subject research that: (1) occurred after July 2004; and (2) is conducted or supported by HHS. As a result, the findings, questions and concerns listed below only relate to IRB activities for which OHRP has jurisdiction.

Based on the information submitted, OHRP makes the following determinations:

(1) It was alleged that UC Berkeley failed to have written IRB procedures that adequately describe the activities outlined in HHS regulations at 45 CFR 46.103(a), 45 CFR 46.103(b)(4) and 46.103(b)(5). In response to this allegation, UC Berkeley made the following statement in its September 20, 2006 response:

> "With regard to the first allegation, the [Committee for the Protection of Human Subjects] CPHS [the UC Berkeley IRB] has a set of written procedures that were most recently updated on November 28, 2000. We have included as **Appendix 1** a copy of the current Committee for Protection of Human Subjects Policies and Procedures document. This document, along with the CPHS Guidelines (**Appendix 2**) and the associated Multiple Project Assurance (**Appendix 16**) effective August 17, 2000, which are referenced in the Policies document, comprise UC Berkeley's written IRB procedures."

In addition, UC Berkeley stated the following:

> "We understand that our written procedures need to be updated and that a general review of our work is appropriate. A decision to undertake this review was made at our August 4, 2006 IRB meeting shortly before your letter of August 7 was received, as noted in the August 4 Meeting Minutes enclosed with this letter. This work is now in progress and the following timetable has been established:
>
> - An updated draft policies and procedures document will be completed by the end of the fall semester.

- An overall review of the work of the CPHS and any necessary changes to the policies and procedures document will be completed by the end of the spring semester."

In response to this information, OHRP requested, and UC Berkeley provided, a *draft* CPHS Policies and Procedures Document.

Prior to making the findings noted below, OHRP reviewed the Committee for Protection of Human Subjects Policies and Procedures Document and the CPHS Guidelines - two of the three documents that comprise UC Berkeley's current written policies and procedures; OHRP did not review the UC Berkeley's MPA when assessing the adequacy of UC Berkeley's current policies and procedures because the MPA has been deactivated. OHRP notes that UC Berkeley identified various sections within CPHS documents where the written IRB procedures required by HHS regulations at 45 CFR 46.103(a) and 45 CFR 46.103(b)(4) and (b)(5) could allegedly be located. OHRP reviewed the referenced sections, but found that in most instances UC Berkeley directed OHRP to sections of CPHS documents that did not include the written procedures as identified. See explanation provided below. In addition, OHRP reviewed relevant sections of the draft CPHS Policies and Procedures Document - the document intended to update/replace the documents that currently comprise UC Berkeley's written policies and procedures. OHRP identified relevant sections of the draft document that could correct, in whole or in part, the findings noted below.

(a) The procedures which the IRB will follow for conducting its initial review of research.

UC Berkeley directed OHRP to the CPHS Polices and Procedures Document (§ VI.) and the CPHS Guidelines Document (§ V.F.) for the procedures referenced above. OHRP reviewed these sections and found that the sections do not discuss such procedures; rather the CPHS Polices and Procedures Document (§ VI.) discusses Continuation Review and the CPHS Guidelines Document (§ V.F.) discusses Continuing Research. As a result, OHRP finds that UC Berkeley does not currently have written IRB procedures that adequately describe the procedures which the IRB will follow for conducting its initial review of research.

Corrective Action: OHRP acknowledges that UC Berkeley has drafted standard operating procedures (SOPs) numbered SOP: RR 401 - Initial Review and SOP: RR402 – Expedited Review which address the procedures the IRB will follow for conducting its initial review of research, i.e., either expedited review or full board review. OHRP finds that these draft SOPs, when finalized, will adequately address the above finding, i.e., failure to have written IRB procedures that adequately describe the procedures which the IRB will follow for conducting its initial review of research.

OHRP notes that both draft SOPs only reference the return of the approved-stamped English Informed Consent document (if any) to the investigator upon IRB approval. OHRP recommends that all IRB-approved informed consent, parental permission, and assent documents be returned to the investigator upon approval.

Required Action: Once finalized, please provide OHRP with the final versions of SOP: RR 401 and RR 402.

(b) The procedures which the IRB will follow for conducting its continuing review of research.

UC Berkeley directed OHRP to § IX.C.(2)(b) of the CPHS Polices and Procedures Document and § V.F. of the CPHS Guidelines Document for the above-referenced procedures. OHRP reviewed the CPHS Polices and Procedures Document (§ IX.C.(2)(b)) and found that this section does not discuss continuing review procedures; rather it discusses minutes of CPHS meetings. OHRP reviewed the CPHS Guidelines Document (§ V.F.) and finds that this section adequately describes the procedures which the IRB will follow for conducting its continuing review of research. Thus, OHRP finds that UC Berkeley currently has the above-referenced written IRB procedures.

Corrective Action: OHRP acknowledges that UC Berkeley has drafted SOP: RR 403 - Continuing Review. OHRP finds that this draft SOP, in addition to the procedures outlined in the CPHS Guidelines Document, adequately describes the procedures the IRB will follow for conducting its continuing review of research. OHRP assumes that this draft SOP is intended to replace the continuing research procedure outlined in the CPHS Guidelines Document.

OHRP has the following comments regarding this draft SOP:

i. The criteria regarding permitting participation in the research beyond the expiration date is misplaced. According to the draft SOP, participation may continue beyond the expiration date for a reasonable amount of time **if subjects participating in the study would suffer a hardship** should participation be discontinued. Please note that OHRP has previously stated that if an investigator has failed to provide continuing review information to the IRB or the IRB has not reviewed and approved a research study by the continuing review date specified by the IRB, the research must stop, unless it is **in the best interest of currently enrolled subjects** to continue participating in the research interventions or interactions.

ii. The draft SOP only references the approved-stamped English Informed Consent document (if any). OHRP recommends that all IRB-approved informed consent, parental permission, and assent documents be returned to the investigator upon approval.

iii. The Continuing Review – Full Board section infers that secondary reviewers are always required, but this is not explicitly stated.

Required Action: Once finalized, please provide OHRP with the final version of SOP: RR 403.

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

OHRP notes that § I.C. of the CPHS Polices and Procedures Document discusses notifying researchers regarding their responsibility for knowing and complying with CPHS requirements; this section does not discuss the procedures that the UC Berkeley IRB follows for reporting its findings and actions to investigators and the institution. OHRP notes that § V.F. of the CPHS Guidelines Document only discusses the procedures that the UC Berkeley IRB follows for reporting its continuing review approval to investigators. Thus, OHRP finds that UC Berkeley does not currently have written IRB procedures that adequately describe the procedures that the IRB will follow for reporting its findings and actions (e.g., regarding conditions of approval, proposed modifications, etc.) to investigators and the institution.

Corrective Action: OHRP notes that UC Berkeley drafted SOP RR:401 – Initial Review; SOP RR:402 – Expedited Review; and SOP RR:403 – Continuing Review. OHRP finds that these draft SOPs fail to address how the IRB notifies the institution in writing of its decision to approve or disapprove the proposed activity as required by 45 CFR 46.109(d).

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

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

UC Berkeley directed OHRP to the CPHS Policies and Procedures Document § VI.A. and to the CPHS Guidelines Document § VI.C. for the procedures the UC Berkeley IRB follows for determining which projects require review more than annually. OHRP reviewed these sections and found that the sections do not contain such procedures. For instance, §

VI.A. of the CPHS Polices and Procedures Document provides the following statement (vs. providing procedures): "The CPHS shall determine which projects will require Committee review more often than annually." In addition, the CPHS Guidelines Document § VI.C. does not address the above-referenced procedures; rather it contains a list of CPHS criteria for approving a project. As a result, OHRP finds that UC Berkeley does not currently have the above written IRB procedures.

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

(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.

In response to this allegation, UC Berkeley did not identify any section of the CPHS Policies and Procedures Document or the CPHS Guidelines Document for the procedures the UC Berkeley IRB follows for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review. As a result, OHRP finds that UC Berkeley does not currently have the above-referenced written IRB procedures. OHRP acknowledges, however, that UC Berkeley has drafted SOP: QA 903 – Site Visits and Third Party Verification. Please note that OHRP did not review this SOP because section 3 of the copy provided was incomplete, i.e., when photocopied only the first paragraph of that section was captured.

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

(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.

UC Berkeley directed OHRP to the CPHS Polices and Procedures Document § V.E. and the CPHS Guidelines Document § VI.D. for these procedures. OHRP notes that these sections do not discuss such

procedures; rather § V.E. of the CPHS Polices and Procedures Document discusses procedures for expedited review and § VI.D. of the CPHS Guidelines Document discusses reporting. Thus, OHRP finds that UC Berkeley does not currently have written IRB procedures that adequately describe 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.

Corrective Action: OHRP acknowledges that UC Berkeley has drafted SOP: RR 404 – Amendment Requests. OHRP finds that this draft SOP, when finalized, will adequately address the above finding, i.e., failure to have written IRB procedures that adequately describe 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 the following in reference to this draft SOP:

i. The SOP only references the approved-stamped English Informed Consent document (if any). OHRP recommends that all IRB–approved informed consent, parental permission, and assent documents that have been modified as a result of the modification request be returned to the investigator upon approval.
ii. The amendment Review – Full Board section references renewal requests when the SOP covers amendment requests.

Required Action: Once finalized, please provide OHRP with the final versions of SOP: RR 404.

(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.

UC Berkeley directed OHRP to the CPHS Polices and Procedures Document § X.C. for the above-referenced prompt reporting procedures. OHRP reviewed this section and notes that the section discusses reporting of adverse events only; it does not contain procedures for reporting serious

or continuing noncompliance with 45 CFR Part 46, serious or continuing noncompliance with the requirements or determinations of the IRB, suspension or termination of IRB approval (resulting from events other than adverse events) or for reporting unanticipated problems that are not adverse events. OHRP also reviewed the CPHS Guideline Document § VI.D.. OHRP notes that this section is a modified reiteration of the federal regulations regarding the reporting of certain events; this section does not contain detailed 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. Thus, OHRP finds that UC Berkeley does not currently have written IRB procedures that adequately describe the procedures which the IRB will follow for ensuring prompt reporting of events as outlined above.

Corrective Action: OHRP acknowledges that UC Berkeley has drafted SOP: RR 408 – Adverse Event Reporting and SOP: RR 409 – Suspension or Termination of a Protocol. Please note that OHRP did not review SOP 408 given the notation included in the draft SOP "Note this needs to be reviewed against the latest OHRP guidance that was recently released." OHRP did, however, review SOP 409 and find that this draft SOP does not address reporting IRB suspensions or terminations to appropriate institutional officials, department or agency heads and OHRP in accordance with 45 CFR 46.103(a), 45 CFR 46.103(b)(5) and 45 CFR 46.113. OHRP could not locate any other draft SOP where such reporting was described.

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

(2) It was alleged that the UC Berkeley IRB, the CPHS, failed to obtain sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. In specific, it was alleged that the study *Unpacking the Paradox of Ingroup Derogation Via Dialecticism, Power, and Affect* (Study 2005-3-37) was approved without IRB review of the pertinent survey instruments.

Based on the explanation of OHRP's jurisdiction provided above, OHRP makes no finding regarding this allegation specific to *Unpacking the Paradox of Ingroup Derogation Via Dialecticism, Power, and Affect*, to which UC Berkeley's FWA does not apply.

After reviewing UC Berkeley's September 20, 2006 response letter, OHRP requested additional information regarding various studies, including *Follow-up of the Multimodal Treatment Study of Children with ADHD: MTA Study* (Study 2004-3-6). OHRP reviewed the IRB file for this study and found no evidence that the study assessment tools/behavior rating checklists (collectively referred to as survey instruments) were reviewed by the CPHS prior to approving/re-approving the study. OHRP noted the following prior to making this finding:

(a) A CPHS review sheet, dated February 25, 2001, stated the following:

> "[Staff: Do we have the full instrument packet? JWL].
>
> The assessment battery includes some measures approved in previous studies with these subjects … . Other instruments will be introduced for these follow-up assessments. It would help to have Professor Hinshaw clarify: (1) Which instruments will be newly introduced for this study during the time when adolescent subjects are still under the age of 18, and the relative sensiitivity [sic] of items in those instruments (note that for students under 18, parents will be asked to complete the DISC-IV, but it is not clear why); (2) What instruments will be introduced as the subjects reach adulthood?"

(b) The Protocol Summary General Versions dated January 30, 2001, January 30, 2003 and January 30, 2004 provide a brief description for each of the study assessments that will be used in the study followed by a statement that "The extensive assessment battery is available upon request."

(c) There is no mention of any of the survey instruments in any of the meeting minutes regarding the study or in documentation associated with review of the study; and

(d) Only certain revised survey instruments (all with 2007 version dates) could be located in the IRB file. It appears that these survey instruments were provided to CPHS as a result of the investigator replacing "several measures (appropriate for adolescents) with versions appropriate for young adults … ." See March 9, 2007 memorandum from principal investigator to CPHS. OHRP notes, however, that previous versions of these revised survey instruments, as well as the other non-revised survey instruments, could not be located in the IRB file.

OHRP is concerned about this failure to review individual survey instruments given statements regarding some of the survey instruments, e.g., "To date, there has been no formal validity testing of the Diagnostic Interview Schedule for Children (DISC-IV);" "The C-DIS-IV **will be obtained** *(emphasis added*)

through Washington University in St. Louis;" "Like other self-rating scales for Children, the Children's Depression Inventory yields high levels of false-positive ratings." OHRP is also concerned given the subject matter associated with certain survey instruments, e.g., Substance Use Questionnaire; Alabama Parenting Questionnaire (APQ) (an assessment tool that measures parenting practices across five domains, including corporal punishment); and Services Use in Children and Adolescents-Parent Interview (SCA-PI); Service Barriers and Attitudes (an assessment tool that was developed for the main MTA study, but has recently been revised/refined to include tracking of aggression, delinquency, and need for court, police, and correctional services, an important follow-up domain in view of the known risk for later antisocial behavior in children diagnosed with ADHD, especially those with comorbid ODD/CD, as found in half the MTA sample). See Protocol Summary General Version 1/30/01, pages 7 – 11.

Required Action: Please provide OHRP with a corrective action plan outlining how UC Berkeley will ensure that CPHS reviews survey instruments prior to approving/re-approving research involving the use of such instruments. Survey instruments need to be taken into consideration when making the determinations required for approval of research under HHS regulations at 45 CFR 46.111.

(3) It was alleged that CPHS failed to make required findings under 45 CFR part 46, subpart D (Additional Protections for Children Involved as Subjects in Research) when reviewing research involving children. In specific, it was alleged that the following studies involved children as subjects without IRB review under subpart D:

(a) Study 2005-5-36;
(b) Study 2005-5-2;
(c) Study 2004-9-31; and
(d) Study 2004-12-38.

UC Berkeley made the following statement in its September 20, 2006 response to the above-referenced allegation:

> "The University of California policy on the protection of human subjects in research requires the application of HHS regulations set forth at 45 CFR 46 to all research involving human subjects, as defined by these regulations, regardless of source of funding. It is therefore the practice of the IRB to review studies involving children as subjects under Subpart D: Additional Protections for Research Involving Children. However, we do not specify in our federal wide assurance that we will apply 45 CFR 46, or its subparts, to research that is funded by non-federal monies. In the course of our investigation, we discovered one instance where the IRB failed to make the required findings under Subpart D. This failure reflects a deviation from university policy; nevertheless,

the failure does not constitute "non-compliance" with federal policy since the study was conducted using non-federal funds. Please find below responses specific to each study cited above."

Based on the explanation of OHRP's jurisdiction provided at the beginning of this letter, OHRP only investigated allegations specific to study *Labor Supply and Compensating Differentials for Commercial Sex Workers in Kenya* (Study 2005-5-2), to which the UC Berkely FWA applies. OHRP notes that Study 2005-5-2 did not involve subjects under the age of 18; therefore, the IRB did not need to make findings under subpart D in order to approve this study. As a result, OHRP finds that the allegations could not be substantiated.

Given that the allegation regarding failure of the IRB to make subpart D findings was a global allegation, i.e., CPHS routinely failed to make such findings when reviewing research involving children, OHRP reviewed the IRB file for study *Follow-up of the Multimodal Treatment of Study of Children with ADHD* (Study 2004-3-6). OHRP found little evidence that the CPHS made the required findings under subpart D when reviewing this study. In fact, OHRP notes that there is no documentation demonstrating that CPHS made subpart D findings at initial IRB review in 2001 and at 2002, 2003, 2004 and 2005 continuing reviews. OHRP does note, however, that the issue of subpart D findings was mentioned in an undated summary update document regarding this study. In specific, the summary update document provides the following: "5. For any protocol involving children, the IRB must determine which of the four categories of permissible research with children, under 45 CFR 46, apply to that study, if any. OHRP recommends that the IRB document the rationale for this choice. Please refer to the attached worksheet outlining permissible research with children." In addition, OHRP notes that the February 2, 2006 CPHS meeting minutes reflect subpart D determinations; this is the first time such subpart D determinations were documented in CPHS meeting minutes. Based on the above, OHRP finds no evidence that the CPHS made subpart D findings when reviewing study #2004-3-6 in 2001, 2002, 2003, 2004 and 2005.

Required Action: Please provide OHRP with a corrective action plan outlining how UC Berkeley will ensure that CPHS makes the required findings under subpart D when reviewing research involving children. In addition, please review all currently active research studies involving children and receiving HHS support to determine whether subpart D findings were appropriately made for those studies. If subpart D findings were not made, CPHS must re-review all such studies for compliance with subpart D. Please provide OHRP with a summary of your findings.

(4) It was alleged that CPHS failed to make required findings under 45 CFR part 46, subpart B (Additional Protections for Pregnant Women, Human Fetuses and Neonates) when reviewing research involving pregnant women. In specific, it was

alleged that study 2004-12-38 included pregnant subjects without IRB review under subpart B.

Based on the explanation of OHRP's jurisdiction provided at the beginning of this letter, OHRP did not investigate allegations specific to this study, to which the UC Berkeley FWA does not apply.

(5) HHS regulations at 45 CFR 46.110(b)(1) limit the use of expedited review procedures to specific research categories published in the *Federal Register* at 63 FR 60364—60367. See http://www.dhhs.gov/ohrp/humansubjects/guidance/expedited98.htm. Category (2) states the following, in relevant part:

Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows: … (b) from … children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

OHRP finds 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). OHRP notes that an undated protocol summary, which appears to be the protocol upon which initial CPHS approval was granted[1], was unclear regarding the amount and frequency of blood to be collected during the study.[2] OHRP notes, however, that a subsequently approved protocol summary/parental permission form clarified the amount and frequency of blood to be collected during the study. Of note, the updated protocol summary provided the following:

Procedures directly involving human subjects:

> "The HIMJR and MOH norms require the following procedures, which are also necessary for the proposed study: a) acute phase samples for viological testing, complete blood count (CBC) with platelets, and transaminase test upon presentation, b) an epidemiological questionnaires upon presentation, c) daily CBC with platelets for hospitalized patients, d) clinical data collection using standardized forms (see Appendix C), e) serological sample upon discharge, f) a convalescent follow-up visit 1-2 weeks following discharge, and g) adherence to norms for patient care.

[1] OHRP assumes that the August 4, 2005, CPHS approval was based on this undated protocol summary given that this is the only protocol summary that could be located in the IRB file that was modified in response to recommendations noted in a CPHS email dated August 1, 2005.
[2] OHRP believes that this uncertainty was based on the fact that the IRB-approved protocol summary/parental permission form failed to include information relating to how long subjects were expected to participate in the study.

> Procedures unique to the study will be the following: a) all parents of patients, and patients 5 years and older, will undergo the consent and assent process, respectively, b) patients will be asked to give 5cc more blood than usual (an additional needle stick is not expected to be necessary), c) outpatients will be asked to return for daily clinical assessment and testing and a convalescent visit, and d) at the convalescent phase visit, 5 cc of blood will be collected."

The IRB approved parental permission form provided the following:

> "A doctor will perform a routine medical examination of your child, and this information will be recorded. Whether your child is hospitalized or allowed to return home, **each day tests will be performed** to better follow his/her illness. Participation in this study does not require any extra needle sticks **during the course of the illness**. However, **a small amount of extra blood (5 cc) will be taken while your child is being treated for dengue**. Two weeks after your child leaves the hospital or recovers from illness, we ask that he/she return for a blood sample (5 cc). We need this extra sample to verify that your child had dengue. Therefore, the length of participation in this study is during your child's illness, usually 5 days, and then one visit two weeks later."

OHRP finds that the undated protocol summary clarifies that the study did not qualify under category (2) given that blood collection is occurring more frequently than two times per week, i.e., a small amount of extra blood (5 cc) will be collected for research purposes on a daily basis for up to five days.

Required Action: Please provide OHRP with a corrective action plan outlining how UC Berkeley will ensure that CPHS appropriately applies expedited review categories to research proposed for initial and continuing review.

(6) OHRP finds that the informed consent document reviewed and approved by CPHS on August 4, 2005 for *Prospective Hospital-Based Study of Dengue Classification and Case Management in Nicaragua* (Study 2005-5-35) failed to include a statement regarding the expected duration of the subject's participation in the research as required by 45 CFR 46.116(a)(1). OHRP notes, however, that CPHS approved a subsequent informed consent document on November 9, 2005 that contained the missing information. OHRP is concerned, however, that it appears as if the initially approved informed consent form was revised by the investigator to address an amendment; not in response to a CPHS request to correct the omission.

Required Action: Please provide OHRP with a corrective action plan outlining how UC Berkeley will ensure that CPHS only approves informed consent forms that contain all of the elements outlined in HHS regulations at 45 CFR 46.116.

(7) OHRP finds that the CPHS study file for *Prospective Hospital-Based Study of Dengue Classification and Case Management in Nicaragua* (Study 2005-5-35) failed to include the following information as required by 45 CFR 46.115(a)(1):

(a) CPHS approved Spanish version (albeit non-stamped) informed consent forms associated with the approval memorandum dated August 4, 2005, amendment approval memoranda dated November 9, 2005 and June 29, 2006 and study renewal memorandum dated September 14, 2006;

(b) CPHS approved assent script(s) associated with the amendment approval memoranda dated November 9, 2005 and June 29, 2006; and

(c) CPHS approved assent form to be used for obtaining written assent from subjects 12 or older.

OHRP notes that the obtaining of written assent for subjects 12 or older was first mentioned in the protocol summary submitted to CPHS in early 2006. OHRP reviewed the documents associated with the March 2, 2006 approval amendment memorandum and the September 14, 2006 renewal letter and could not locate the CPHS-approved written assent form.

Required Action: Please provide a corrective action plan outlining how UC Berkeley will ensure that CPHS maintains study files that contain all the information outlined in HHS regulations at 45 CFR 46.115.

(8) HHS regulations at 45 CFR 46.115(a) require that the institution prepare and maintain adequate documentation of IRB activities. OHRP finds that it was difficult to reconstruct a complete history of all IRB actions related to the review and approval of *Prospective Hospital-Based Study of Dengue Classification and Case Management in Nicaragua* (Study 2005-5-35). In specific, OHRP could not determine what action CPHS took in reference to documentation submitted along with a CPHS Application Cover Sheet, signed December 26, 2005, which indicated a study amendment; OHRP could find no Study Amendment Form accompanying the CPHS Application Cover Sheet. Instead, OHRP found an undated document entitled "Cellular Tropism of Dengue Virus In Vivo – Request for CPHS Exemption #4." In addition, there were multiple copies of various amendment requests in various sections of the IRB file without any explanation as to what bearing, if any, these previously approved amendment requests had on the request currently under consideration. OHRP could not find written documentation of CPHS approval for every amendment request, i.e., approval of new key personnel, approval of NIH as a new funding source (prior approval was withdrawn until an FWA was obtained by one of the participating sites). Lastly, OHRP notes that a study amendment request, dated August 11, 2006, was never processed. OHRP could find no explanation as to why the request was not processed.

Required Action: Please provide OHRP with a corrective action plan outlining how UC Berkeley will ensure that CPHS maintains study files that contain adequate documentation of IRB activities, as required by HHS regulations at 45 CFR 46.115.

(9) Continuing review of research must be substantive and meaningful. HHS regulations at 45 CFR 46.111 set forth the criteria that must be satisfied in order for the IRB to approve research. These criteria include, among other things, determinations by the IRB regarding risks, potential benefits, informed consent, and safeguards for human subjects. The IRB must ensure that these criteria are satisfied at the time of both initial and continuing review. The procedures for continuing review by the convened IRB may include a primary reviewer system.

In conducting continuing review of research not eligible for expedited review, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research, including: (i) the number of subjects accrued; (ii) a summary of adverse events and any unanticipated problems involving risks to subjects or others and any withdrawal of subjects from the research or complaints about the research since the last IRB review; (iii) a summary of any relevant recent literature, interim findings, and amendments or modifications to the research since the last review; (iv) any relevant multi-center trial reports; (v) any other relevant information, especially information about risks associated with the research; and (vi) a copy of the current informed consent document and any newly proposed consent document.

At least one member of the IRB (i.e., a primary reviewer) also should receive a copy of the complete protocol including any protocol modifications previously approved by the IRB. Furthermore, upon request, any IRB member also should have access to the complete IRB protocol file and relevant IRB minutes prior to or during the convened IRB meeting. The minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

OHRP finds 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. OHRP notes a lack of information and/or numerous discrepancies among the various protocol continuation/renewal forms submitted for this study. In specific, OHRP notes the following:

(a) Continuation/renewal forms, dated February 20, 2002 January 30, 2003 and January 29, 2004, contained limited information regarding the number and description of subjects who participated during the last year. According to these continuation/renewal forms, the investigator only enrolled control and ADHD adolescents during the first three years of the study; the investigator did not enroll any parents during this timeframe.

According to the CPHS approved study design, the investigator could not enroll any child in research until the investigator obtained parental permission/informed consent from the child's parent(s). The CPHS approved parental consent forms for this study served a dual purpose; the consent form sought to obtain parental permission from the parents (to study his/her child) and informed consent from the parent for his/her participation in the study, e.g., completion of questionnaires/surveys regarding parents activities, feelings, etc. See 45 CFR 46.111(a)(3) and (4).

(b) Continuation/renewal form, dated January 3, 2005. This was the first continuation/renewal form that referenced both adolescents and families as individuals who participated in the study. CPHS should have noted this change in reporting and should have queried the investigator about the change. See 45 CFR 46.111(a)(4).

(c) Conflicting information contained in the following continuation/renewal forms, which was never identified by CPHS:

	December 6, 2005	**December 14, 2006**
Total # of Participants Consented and Enrolled in Research Protocol to Date:	149	131
# of Subjects Who Withdrew Voluntarily	17	0

See 45 CFR 46.111(a)(4) and (6).

Required Action: Please provide OHRP with a corrective action plan outlining how UC Berkeley will ensure that CPHS conducts substantive and meaningful continuing review that considers all elements required by HHS regulations at 45 CFR 46.111.

(10) OHRP finds that CPHS approves 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. OHRP notes that when the convened IRB requests clarifications or modifications regarding the protocol, including, but not limited to, informed consent documents, recruitment materials, or the investigational brochure, that are required by the IRB to make the necessary determinations in order to approve research, IRB approval of the proposed research must be deferred, pending subsequent review by the convened IRB of responsive material. In specific, OHRP finds the following:

(a) CPHS approved the study *Sex Work as a Response to Risk in Kenya* (formerly Labor Supply and Compensating Differentials for Commercial Sex Workers in Kenya) (Study 2005-5-2) contingent upon substantive modifications or clarifications that were directly relevant to the 45 CFR 46.111 determinations without requiring additional review by the convened IRB. CPHS conditionally approved the above-referenced study even though CPHS noted that the protocol contained little information regarding:

(i) Ensuring that 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 (namely, sample size);
(ii) Equitable selection of subjects (namely, subject recruitment and enrollment procedure); and
(iii) Informed consent (how sought and documented).

See August 5, 2005 Conditional Approval Letter.

(b) CPHS approved the study *Follow-up of the Multimodal Treatment of Study of Children with ADHD* (Study 2004-3-6) contingent upon substantive modifications or clarifications that were directly relevant to the 45 CFR 46.111 determinations without requiring additional review by the convened IRB. OHRP notes that, on more than one occasion, the CPHS conditionally approved the study even though the IRB noted that the protocol contained little information regarding:

(i) Risks to subjects and how they are minimized (by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk);
(ii) Whether the 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;
(iii) Equitable selection of subjects (namely, subject recruitment and enrollment);
(iv) Whether informed consent needed to be sought from the roommates and/or supervisors of the enrolled subjects; and if informed consent was required from such individuals, how informed consent would be sought and documented); and
(v) The provisions to protect the privacy of subjects and maintain the confidentiality of data

See February 2 and 27, 2007 Conditional Approval Letters.

Required Action: Please provide OHRP with a corrective action plan outlining how UC Berkeley will ensure that CPHS only approves research after the

convened IRB has reviewed information that is relevant to the determinations required by the IRB under HHS regulations at 45 CFR 46.111.

(11) 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. 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 later 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 finds that CPHS failed to conduct continuing review of research at least once per year for the study *Follow-up of the Multimodal Treatment of Study of Children with ADHD* (Study 2004-3-6). In specific, OHRP notes that CPHS granted conditional re-approval for the study at its February 7, 2003 meeting; with final approval granted by the CPHS Chair on April 4, 2003. OHRP notes further that the CPHS did not re-review and approve the study again until March 6, 2004; more than one year following the last IRB review and approval of February 7, 2003.

Required Action: Please provide OHRP with a corrective action plan outlining how UC Berkeley will ensure that CPHS conducts continuing review of research at intervals appropriate to the degree of risk, but not less than once per year. In addition, please make sure that the corrective action plan addresses how UC Berkeley will ensure that CPHS appropriately calculates the next continuing review date when the convened IRB specifies conditions for approval that are to be verified as being satisfied by the IRB Chair or another IRB member designated by the Chair.

(12) OHRP finds that the informed consent documents reviewed and approved by the CPHS for study *Sex Work as a Response to Risk in Kenya* (Study 2005-5-2) failed to include and adequately address the following elements required by HHS regulations at 45 CFR 46.116(a):

(a) Section 46.116(a)(2): A description of any reasonably foreseeable risks and discomforts (i.e., risks and discomforts not described).

(b) Section 46.116(a)(3): A description of any benefits to the subject or others that may reasonably be expected from the research.

(c) 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. OHRP notes that CPHS

approved an informed consent document that referenced a separate document containing the required contact information in lieu of requiring the informed consent document to contain such information.

Please note that HHS regulations at 45 CFR 46.116(d) require that an IRB find and document four specific criteria when approving waiver or alteration of some or all of the required elements of informed consent. OHRP finds no evidence demonstrating that CPHS found and documented such criteria prior to approving the informed consent document for this study, which did not include two elements of informed consent, i.e., 46.116(a)(2) and (a)(3), and which altered one element of informed consent, i.e., 46.116(a)(7).

In addition, OHRP finds that all the parent subject consent documents[3] approved by CPHS for the study *Follow-Up of the Multimodal Treatment Study of Children with ADHD* (Study 2004-3-6) in 2001 failed to include 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 as required by HHS regulations at 45 CFR 46.116(a)(7). OHRP notes that the parent subject consent documents were approved by the IRB in 2001 even though the designated IRB reviewer for the study noted in his/her CPHS Reviewer's Informed Consent Checklist, dated 2/9/01, the following in reference to the informed consent documents: "Question: Is a contact given for questions about rights or treatment as research subjects? Answer: N."

Required Action: Please provide OHRP with a corrective action plan outlining how UC Berkeley will ensure that the CPHS only approves informed consent documents that adequately address the elements listed in HHS regulations 45 CFR 46.116(a) unless appropriately waived/altered by CPHS.

OHRP has the following questions and concerns regarding the above-referenced studies:

(13) [Redacted]

[3] As stated previously, the CPHS approved parental consent form for this study served a dual purpose; the consent form sought to obtain parental permission from the parent (to study his/her child) and informed consent from the parent for his/her participation in the study.

[Redacted]

(14) [Redacted]

[Redacted]

[Redacted]

(15) [Redacted]

(16) [Redacted]

(17) [Redacted]

(18) [Redacted]

(19) [Redacted]

(20) [Redacted]

(20) [Redacted]

OHRP has the following questions and concerns regarding UC Berkeley's system for protecting human subjects:

(21) [Redacted]

[Redacted]

(22) [Redacted]

[Redacted]

(24) [Redacted]

(25) [Redacted]

[Redacted]

(26) [Redacted]

(27) [Redacted]

(28) [Redacted]

At this time, OHRP provides the following guidance:

(29) OHRP notes that none of the protocols or informed consent forms that were approved by CPHS for Study 2005-5-35 and Study 2004-3-6 contained version dates or other identifying information. As a result, in many instances it was difficult for OHRP to identify which protocol and/or informed consent form was

associated with a particular CPHS approval memorandum. Given this difficulty, and in an attempt to avoid confusion by IRB members, IRB staff, and investigators regarding which version of a document had been approved by CPHS, OHRP recommends that CPHS require that investigators include version dates (or other identifying information) on all protocols, informed consent forms, or other documents requiring IRB approval

OHRP provides the following guidance in reference to UC Berkeley's draft Policies and Procedures Document:

(30) Many of the draft CPHS Policies and Procedures still lack operational detail in that many of the draft policies and procedures do not provide sufficient step-by-step operational details that would allow an independent observer to understand how the CPHS operates and conducts its major functions. See OHRP's Guidance on Written IRB Procedures, available at http://www.hhs.gov/ohrp/humansubjects/guidance/irbgd107.htm;

(31) SOP: GA 102 - Training and Education Policy and Procedures.

(a) The use of the term "Voting IRB Members" infers that there are non-voting IRB members. Please note that there is no such entity as a non-voting IRB member under HHS regulations at 45 CFR part 46. This comment is also applicable to SOP: OR 203 - Duties of IRB Members.

(b) Please note that there is no such entity as an Ex-Officio IRB member under HHS regulations at 45 CFR part 46. OHRP recommends including a definition section regarding IRB members, alternates, IRB consultants, etc.

(32) SOP: GA 104 - IRB Member Conflict of Interest. OHRP recommends that this policy clarify whether the IRB member must remove him/herself during study deliberations/discussions or is permitted to remain during such deliberations/discussions, but not participate in those deliberations/discussions. OHRP recommends that this clarification also be included in SOP: FO 303.

(33) SOP: OR 201 - Composition of the IRB.

(a) This SOP, which references regular members, leads the reader to believe there is another category of IRB members, (i.e., non regular members); however, the SOP does not follow up with such a differentiation. Please note that HHS regulations at 45 CFR part 46 makes no such differentiation. OHRP notes that while the draft SOP refers to a nonaffiliated IRB member, the draft SOP does not contain a definition for that term. Thus, OHRP suggests including such a definition. OHRP has provided the following guidance regarding the term affiliated and non-affiliated:

An employee or agent of the organization registering the IRB/IEC (or a member of that person's immediate family) is considered affiliated. Affiliated members include, but are not limited to individuals who are: part-time employees; current students; members of any governing panel or board of the institution; paid or unpaid consultants; healthcare providers holding credentials to practice at the institution; and volunteers working at the institution on business unrelated to the IRB/IEC. An individual that has no affiliation with the organization registering the IRB/IEC, other than as an IRB/IEC member, is considered unaffiliated with the entity operating the IRB/IEC. Unaffiliated members may include people whose only association with the institution is that of a patient, subject, or former student at that institution.

(b) OHRP notes that here is no definition for alternate IRB member even though the SOP references such a member. OHRP acknowledges that HHS regulations at 45 CFR part 46 do not address the designation of alternate IRB member; however, for many years OHRP has permitted organizations to identify alternate members for primary members. When reviewing rosters that include alternate members OHRP assumes that, in general, with respect to the capacity in which the primary IRB member was intended to serve, each alternate IRB member has experience, expertise, background, professional competence, and knowledge comparable to that of the primary IRB member whom the alternate would replace. See also SOP: OR 203 - Duties of IRB Members.

(34) SOP: OR 202 - IRB Membership.

(a) There is no mention that IRB members may be appointed based on Faculty Senate recommendations, as stated in SOP:OR 201.

(b) This is the first time the term "IRB Executive Committee" is referenced. There is no explanation relating to this committee, e.g., who is on it; what is the committee's charge, what is the committee's relationship with the IRB, etc.

(35) SOP: FO 302 - Review for a Determination of Exemption.

(a) OHRP suggests rewording this SOP to more closely mirror the regulations. See 45 CFR 46.101(b). OHRP is concerned that the rewording of (B) and (C) may be confusing to the reader. OHRP suggests explaining the term "existing data" so that investigators are aware that existing means existing at the time the proposal is submitted to the IRB for consideration.

(b) It is not clear what would occur if there is disagreement between the IRB chairperson and the IRB administrative staff as to whether a proposed project can be exempt under HHS regulations at 45 CFR 46.101(b). See § 4 – Process Review. OHRP notes that the CPHS written procedures give the human research protections administrator final authority in determining a finding of exempt or to revoke determinations granted by IRB administrative staff; however, OHRP notes that the human research protections administrator is not referenced in § 1.3. IRB Chair involvement is not mentioned in the process review section; however, see § 1.3

(c) OHRP notes that this SOP does not state whether the IRB will review modifications to exempt studies to determine whether the modification would reclassify the research as non-exempt, resulting in the need for IRB review. OHRP suggests that this SOP state CPHS intentions regarding these types of review.

(36) SOP: RR 405 - Monitoring Ongoing Research.

(a) The Revisions of Research Protocols section appears to be simply a reiteration of another policy/procedure. It does not explain how this other procedure has applicability/relevancy to the draft SOP.

(b) OHRP recommends that the responsibility section explain the process, including operational details, for conducting ongoing reviews of research, e.g., criteria for identifying studies, rather than simply provide a statement as to who is responsible for establishing such processes. Please refer to OHRP's Guidance on Written IRB Procedures, available at http://www.hhs.gov/ohrp/humansubjects/guidance/irbgd107.htm

(37) SOP: RR 407 - Categories of Action.

(a) OHRP notes that this SOP appears to be limited in scope, i.e., the IRB may decide to approve or disapprove the proposed research activity, or to specify modifications required to secure IRB approval of the research activity. OHRP notes that the determinations identified in the draft SOP apply to review of modification requests, in addition to initial and continuing review of studies.

(b) OHRP notes that the criteria for disapproval need not be two-fold. In other words, the IRB may disapprove research if the research meets one of the two criteria; it need not meet both criteria.

(c) It would be beneficial to provide more explanation regarding when the approval period begins. For instance, it would be helpful to explain that an approval period begins on the date approval is granted by the convened

IRB; not the date that the IRB chairperson approved the study on behalf of the convened IRB following the submission of requested information.

(38) SOP: RR 408 - Adverse Event Reporting. OHRP did not review this policy/procedure given the following notation included in the draft SOP "Note this needs to be reviewed against latest OHRP Guidance that was recently released."

(39) SOP: RR 409 - Suspension or Termination of a Protocol. OHRP recommends that the SOP explain the following:

(a) How enrolled subjects will be informed when a study, in which they are participating, has been suspended or terminated, e.g., timeframe for informing, method of informing, etc.;

(b) How the determination is made to allow subjects to continue in a study that has been suspended; and

(c) How the request to allow subjects to continue is processed.

(40) SOP: RR 410 – Noncompliance.

(a) OHRP recommends that CPHS spell out the acronym UCOP.

(b) Paragraph 2 is unclear.

(c) The SOP does not mention serious or continuing noncompliance with the Common Rule or the requirements or determinations of the IRB as stated in HHS regulations 45 CFP part 46.103(b)(5)(ii) although there is a reference to such actions under the § 1.3. It is not clear whether these types of noncompliance actions will be handled differently than those simple noncompliance or serious noncompliance.

(d) OHRP recommends that there should be another entity, in addition to OPHS staff, responsible for accepting allegations of noncompliance in the event that an allegation involves an IRB staff member, e.g., IRB staff routinely exempts research when it does not qualify for exemption under HHS regulations 45 CFR 46.101(b). OHRP has the same recommendation regarding § 4 – Process Review.

(41) SOP: SC 501 - Vulnerable Populations: Pregnant Women, Fetuses and Neonates. OHRP notes that § 1.3 of the draft SOP was modified from the current regulatory language. It is not clear whether the rewording of the current regulatory language was intentional and if so, whether the rewording changes what was intended with the regulations.

(42) SOP: SC 502 - Prisoners as a Vulnerable Population.

(a) OHRP recommends that this policy be clear in that it applies to individuals involuntarily confined or detained in a penal institution.

(b) OHRP is unclear as to why the draft policy references "clinical investigation" when the HHS protection of human subjects regulations refer to biomedical and behavioral research, and not clinical investigations.

(43) SOP: SC 503 – Children as a Vulnerable Population. OHRP notes that this draft SOP does not reference the requirements of HHS regulations at 45 CFR 46.409.

(44) SOP: IC 701 – General Requirements and Documentation for Informed Consent.

(a) OHRP suggests that CPHS insert the phrase "and/or" in between the references "45 CFR 46.116(a)" and "21 CFR 50.25." OHRP notes that 45 CFR Part 46 only applies to non-exempt human subject research that is supported or conducted by HHS. OHRP further notes that 21 CFR part 50 only applies to human subject research falling under the jurisdiction of the FDA. Thus, an informed consent document need only satisfy the 45 CFR part 46 and 21 CFR part 50 informed consent requirements when the non-exempt human subject research is supported or conducted by HHS and involves an investigational product for which FDA has jurisdiction.

(b) OHRP suggests that the policy/procedure outline under what circumstances the short form shall be used.

(c) OHRP recommends that the last sentence of §1.5.1 be revised to read as follows: "A signed copy of the document must be given to the participant and/or the person signing the form."

(d) OHRP notes that the IRB must receive all translated versions of the short form document as a condition of approval, but the IRB does not require the same for all translated versions of the full written informed consent form. §1.7.1(ii) simply states "the investigator must submit translations of the final, IRB-approved consent documents for the IRB files as soon as the translations are available."

(45) SOP: IC 702 – Waivers of Informed Consent. OHRP recommends that the policy statement be revised to reflect that an IRB may approve a waiver of informed consent if it finds **and documents** that the research meets specific regulatory criteria. See 45 CFR 46.116(c) and (d).

(46) SOP: IC 703 – Assent and Parental/Guardian Permission. OHRP notes that the reference to §1.3 is misplaced. OHRP notes that §1.6 addresses wards and

references SOP 503 for further guidance regarding wards. OHRP notes, however, that SOP 503 does not address wards as subjects.

Please submit your response to the findings, questions and concerns noted above so that OHRP receives them no later than August 24, 2007. 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. Do not hesitate to contact OHRP if you should have any questions regarding this matter.

Sincerely,

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

cc: Dr. Rebecca D. Armstrong, HPA, UC Berkeley
Dr. Malcolm Potts, IRB Chairperson, UC Berkeley
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Ms. Shirley Hicks, OHRP
Dr. Irene Stith-Coleman, OHRP
Dr. Kristina Borror, OHRP
Dr. Sam Shekar, NIH