DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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Mary Beth Burnside, Ph.D.
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Charles V. Shank, Ph.D.
Director
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RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1554 and Federalwide Assurance FWA-1169

Research Project: National Walkers Health Study
Project Number: 2000-2-73
Principal Investigator: Paul Williams, Ph.D.

Dear Drs. Burnside and Shank:

The Office for Human Research Protections (OHRP) has reviewed the University of California, Berkeley (UCB) and the Lawrence Berkeley National Laboratory (LBL) September 22, 2000 report regarding the above-referenced research that was submitted in response to OHRP's August 7, 2000 letter to UCB and LBL. OHRP apologizes for the delay in responding to your report.

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

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.116(d) require that the Institutional Review Board (IRB) find and document four specific criteria when

approving waiver or alteration of some or all of the required elements of informed consent. OHRP's review of IRB documents reveal no evidence that the IRB satisfied this requirement for the above-referenced research.

Corrective Action: OHRP acknowledges that the UCB IRB is strengthening its documentation requirements by providing more explicit statements of the criteria on which such decisions are made, and a more detailed and complete record of the rationale for altering or eliminating standard elements of informed consent in specific cases such as this. UCB/LBL also is considering a policy limiting the amount of time that research projects may continue to receive expedited reviews to ensure that any changes in regulation, policy, or standards of accepted practice are applied uniformly. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the UCB/LBL FWA.

As a result, OHRP is closing its investigation and anticipates no need for further involvement in this matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

At this time, OHRP provides the following additional guidance:

(2) HHS regulations at 45 CFR 46.116 state that, except as provided elsewhere in the regulations, no investigator may involve a human being as a subject in research covered by the regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. HHS regulations at 45 CFR 46.102(c) define a legally authorized representative as an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. OHRP notes that the NRHS Follow-up Questionnaire approved by the IRB on 9/25/98 allowed for "Signature of next-of-kin, if participant is unable to sign" for permission to release medical information and for informed consent for the follow-up survey. OHRP recommends that UCB/LBL seek advice from legal counsel regarding whether or not under California law a "next-of-kin" is a legally authorized representative who can consent to a subject's participation in such research procedures.

(3) HHS regulations at 45 CFR 46.116(d) state that an IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

(a) the research involves no more than minimal risk to the subjects;

(b) the waiver or alteration will not adversely affect the rights and welfare of the subjects;

(c) the research could not practicably be carried out without the waiver or alteration; and

(d) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

OHRP acknowledges UCB/LBL's statement that the IRB's decision to waive certain elements of informed consent was in compliance with its MPA. However, OHRP notes that the third criterion, that the research could not practicably be carried out without the waiver or alteration, may not have been satisfied for this research. The principal investigator stated that space limitations of the magazines in which some of the surveys were printed prohibited him from including all the elements of informed consent. However, on February 5, 1998, the IRB approved a version of the survey/informed consent that was required by the DOD which included many more of the required elements of informed consent. It is difficult to see how the other surveys would have been impracticable to carry out by including these and other required elements, particularly for the web-based version of the questionnaire, as well as questionnaires that were mailed to subjects, which did not have the same space restraints as those printed in magazines. OHRP strongly recommends that the UCB/LBL IRB ensure, when approving a waiver or alteration of the informed consent requirements for similar research, that the research could not practically be carried out without the waiver or alteration.

(4) OHRP notes that when reviewing protocol applications, the IRB must receive sufficient information to make the determinations required for approval of the proposed research under HHS regulations at 45 CFR 46.111. OHRP notes that the 1996 grant application to NHLBI stated that questionnaires would be sent to selected non-responders to ask why the person did not respond. There is no evidence that the UCB/LBL IRB reviewed and approved this questionnaire. Such questionnaires should be provided to the IRB for review and approval.

(5) HHS regulations at 45 CFR 46.116 state that, except as provided elsewhere in the regulations, no investigator may involve a human being as a subject in research covered by the regulations unless the investigator has obtained the legally effective informed consent of the subjects or the subject's legally authorized representative, under circumstances that minimize the possibility of coercion or undue influence.

OHRP notes that the investigators conducting the above-referenced research were repeatedly sending questionnaires to non-responders unless the questionnaire was returned as "refused." When the IRB required that a statement to this effect be put on the questionnaires, the principal investigator requested that this requirement be removed because he felt that many participants would feel that there is no time urgency to respond and would wait for the next questionnaire to arrive before replying, increasing the cost of the research. This request of the principal investigator was apparently honored, even though the convened IRB stated that the project be approved provided that condition, among others, was met. OHRP recommends that such recruiting practices be reviewed in the light of the possibility for coercion or undue influence.

(6) HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the IRB review and approve **all** proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent

immediate hazards to the subjects. OHRP notes that the principal investigator may not be aware of this requirement. A January 3, 1994 memo from the principal investigator to the chair of the IRB stated "I would benefit from a clearer description of what constitute minor changes that do not require prior approval, and what constitutes significant changes that requires approval from the committee prior to their implementation." OHRP recommends that the IRB provide guidance for the investigator regarding this important request, if it has not already done so.

(7) Written IRB policies and procedures should provide a step-by-step description with key operational details for each of the procedures required by HHS regulations at 45 CFR 46.103(b)(4) and (5):

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

(b) 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.

(c) 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 strongly recommends that the IRB procedures be revised to include these operational details, if this has not already been done.

(8) The minutes of the February 21, 1992 IRB meeting include a discussion of whether the exemption at 45 CFR 46.101(b)(1) could apply to research involving teacher staff meetings. The minutes indicate that use of this exemption for such research would be acceptable "because risks to subjects are minimal." OHRP notes that this particular exemption is only applicable to "research conducted in established or commonly accepted educational settings, involving normal educational practices."

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Kristina C. Borror, Ph.D.

Compliance Oversight Coordinator
Division of Human Subject Protections

cc: Dr. Jane Mauldon, UCB IRB
Ms. Sherry Buckley, Manager UCB, IRB
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