**DEPARTMENT OF HEALTH & HUMAN SERVICES**

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**Office of Public Health and Science**

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February 19, 2009

Bertram Lubin, M.D.
President
Children's Hospital Oakland Research Institute
5700 Martin Luther King Jr. Way
Oakland, CA 94609

**RE: Human Research Subject Protections under Federalwide Assurance (FWA) 0094**

Dear Dr. Lubin:

Thank you for your November 12, 2008 report in response to our September 11, 2008 request that Children's Hospital Oakland Research Institute, California (CHORI) respond to questions and concerns arising from our August 5–7, 2008 on-site evaluation regarding compliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46).

A. Determinations regarding your institution's system for protecting human subjects

(1) HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the institutional review board (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. We determine that a protocol change in protocol #2007-016 involving a consent addendum for subjects who had changed sites was not reviewed and approved by the CHORI IRB until one year after the change was implemented.

**Corrective Action:** We acknowledge that, in the future, the Children's Hospital (CH) IRB will request that subjects be re-consented at the time they change study sites. We interpret this to mean that the CHORI IRB will review and approve consent (or parental permission) addenda before they are implemented by investigators. With this understanding, we determine that this corrective action adequately addresses our determination of noncompliance. We note that "re-consenting" subjects who began participating in a research

study at another institution under an appropriate informed consent or parental permission procedure is not necessarily required under the HHS regulations.

(2) We determine that certain informed consent documents reviewed and approved by the CH IRB failed to include or adequately address the following elements required by HHS regulations at 45 CFR 46.116(a):

(a) Section 46.116(a)(1): a complete description of the procedures to be followed, and identification of any procedures which are experimental (e.g., protocols #2007-11, bone marrow aspirate, whether done for clinical or research care; 2006-046; 2000-32, eyelid surgery; #2006-073, QOL questionnaire and optional blood draw).
(b) Section 46.116(a)(2): A description of any reasonably foreseeable risks and discomforts (e.g., protocol#2006-046, parental permission inadequate description of risks).
(c) Section 46.116(a)(4): A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject (e.g., protocol # 2006-046 bone marrow transplant alternatives outside the research).
(d) Section 46.116(a)(8): A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. (e.g., protocols #2000-32)

Moreover, there was no evidence demonstrating that the IRB approved any waiver or alteration of the informed consent requirements for the above referenced protocols in accordance with 45 CFR 46.116(d).

**Corrective Action:** We acknowledge that the consent forms for the studies referenced above will be revised to describe the necessary elements of informed consent.

**Required Action:** By March 27, 2009 please provide a corrective action to ensure that the CH IRB does not approve informed consent documents that do not include all the required elements of informed consent unless the IRB approves a waiver or alteration of the informed consent requirements in accordance with 45 CFR 46.116(d).

(3) We determine that the CHORI IRB was inconsistent on occasion when it made the findings required for approval of research involving children as required by HHS regulations at 45 CFR 46.405. For example, we noted that, for protocols #2000-32 and 2006-31, the IRB determined that the protocol was approvable under section 46.405; however, the protocol and parental permission document indicated that the research had no direct benefit for subjects.

**Corrective Action:** We acknowledge that the CHORI IRB has requested changes to the informed consent forms to include the prospect of direct benefits.

**Required Action:** By March 27,2009 please provide a corrective action to ensure that the CHORI IRB only approves informed consent documents that are consistent with the protocol and the findings of the IRB under HHS regulations at 45 CFR 46.404-406.

(4) We determine that your November 12, 2008 response adequately addressed concerns (2), (3), (4), (6), (10), (12) and (13) presented in our September 11, 2008 letter.

B. Resolved Concerns

The following concerns we expressed in our September 11, 2008 letter have been adequately addressed by CHORI and the CH IRB; we note these are not violations of the HHS regulations at 45 CFR part 46:

(1) We expressed concern that the CH IRB appeared sometimes to have reviewed insufficient information to make the determinations for approval under HHS regulations at 45 CFR 46.111. In specific, we noted the following:

(a) When the IRB conducted facilitated review of protocols that have been reviewed by the National Cancer Institute Central IRB (CIRB), they appear to have reviewed only minimal information regarding subject recruitment and consent procedures. [protocols #2008-012, 2008-027, 2003-023, 2005-032, 2005-066].
(b) We noted that the CH IRB appeared not to have the background and expertise to review protocol #2000-32 and lacked sufficient information regarding the social, economic, and political status of the subject population in Nepal.
(c) We also noted that the IRB approved a protocol involving a Quality of Life evaluation tool that was not provided to the IRB for review [protocol #2008-048].

**Institution Action:** We acknowledge that the CIRB application form has been revised to solicit information about subject recruitment and consent procedures, and all open CIRB studies have been revised to include this information. We acknowledge that, in the future, the institution will request that outside reviewers with the appropriate expertise are consulted to obtain local context. Please note that external experts may not be required if an internal expert (including the principal investigator) provides the information to the IRB, either in written form, or during an IRB meeting. We acknowledge that, in the case of protocol #2008-048, the protocol indicated that the evaluation tool that had been published had been validated for use in a very similar study as protocol #2008-048. The above corrective actions address our concerns. Please note that the fact that an evaluation tool is "standard" or has been published will in some instances not, by itself, be sufficient information to enable the IRB to determine that such a tool is appropriate for a particular study.

(2) The IRB staff and members expressed concern to us that the current IRB membership lacks the diversity, including consideration of race, gender and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and

counsel in safeguarding the rights and welfare of human subjects, as required under HHS regulations at 45 CFR 46.107(a).

**Institution Action:** We acknowledge that CHORI has asked the hospital office of volunteer services to list the IRB as a volunteer opportunity, has written to the local chapter of AARP and contacted community clubs to recruit additional IRB members, and has asked all IRB members to help recruit new members to expand the diversity of the IRB. This corrective action adequately addresses the concern.

C. Additional Concerns

[Redacted]

Please respond to the above required actions and concerns by March 27, 2009. If you identify any areas of noncompliance in reviewing the above concerns, please describe corrective action that you

have taken or plan to take to address the noncompliance. If you have any questions, or if you need assistance in developing any corrective action plan, please feel free to contact us.

We appreciate 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.
Director, Division of Compliance Oversight

Cc: Denyse Pettersson, CIM, CIP
John R. Waterson, M.D., Ph.D.
Commissioner, FDA
Dr. Joanne Less, FDA
Dr. Sherry Mills, NIH
Mr. Joseph Ellis, NIH