DEPARTMENT OF HEALTH & HUMAN SERVICES

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Frank Tiedemann
President/CEO
Children's Hospital Oakland
747 52nd Street
Oakland, CA 94609

RE: Human Research Subject Protections Under Federalwide Assurance FWA- 94

Research Project: Insights from Transitioning Families Using Focus Groups
Principal Investigator: Cheryl Zlotnick

Research Project: Pilot Study for Pulmonary Complications in Sickle Cell Disease
Principal Investigator: Carolyn Hoppe

Research Project: The Role of Natural Killer Cell Immunoglobulin Receptors and Their HLA Ligands in Unrelated Blood and Marrow Transplants
Principal Investigator: Elizabeth Trachtenberg

Research Project: Search for Type I Diabetes Susceptibility Factors in a Continental Italian Population
Principal Investigator: Janelle Noble

Dear Mr. Tiedemann:

The Office for Human Research Protections (OHRP) has reviewed the Children's Hospital and Research Center of Oakland's (CHRCO) August 15, 2005 letter that was submitted in response to OHRP's July 7, 2005 letter to CHRCO, regarding allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR part 46) involving the above-referenced research.

(1) It was alleged that certain CHRCO institutional review board (IRB) protocol files lacked copies of the protocol and copies of all correspondence between the IRB and investigators. It was also alleged that the CHRCO IRB appears to review only minimal information regarding (a) subject recruitment and enrollment procedures; (b) the

equitable selection of subjects; (c) provisions to protect the privacy of subjects and maintain the confidentiality of data; and (d) additional safeguards to protect the rights and welfare of subjects who are likely to be vulnerable.

HHS regulations at 45 CFR 46.111(a) state that, in order to approve research covered by the regulations, the IRB shall determine that certain requirements are satisfied. OHRP finds that the CHRCO IRB failed to obtain sufficient information about the following protocols to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111:

(a) "Insights from Transitioning Families Using Focus Groups," Cheryl Zlotnick, principal investigator

(i) 45 CFR 46.111(a)(3): Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons. OHRP finds that CHRCO IRB records for the above-referenced research demonstrate a failure of the IRB to obtain sufficient information regarding the selection of subjects.

The above "protocol" was approved on March 12, 2004 via expedited review by the IRB Chair. However, the IRB file does not contain a protocol nor does it contain an IRB application. It contains a one and a half page document that provides an overview of the project but does not provide specific information. For example, it states the following:

> To ensure that we obtain the widest representation of our community, we will make an effort to recruit fifteen consumers/clients with varying backgrounds including ethnicity/race, language preference, educational level, and different parenting experiences. Child care will be provided to free parents who would not otherwise be able to participate...The most important aspect of the focus group is to obtain participation. To further this goal, we will provide food and drinks to facilitate group participation and comfort. Also, participants will receive $30 gift certificates in exchange for their time, transportation and contribution.

There is no explanation of the manner in which participants will be recruited. OHRP notes that the document entitled "Consent to Participate in an evaluation of the CVC using Focus Groups" contains the following statement: "You have been selected by chance from a list of caregivers who have used CVC services." OHRP notes that the reference in the

consent form to selection by chance does not seem to match the statement in the other document. In addition, the one and a half page document states that child care will be provided yet the consent form states, "Unfortunately, we will be unable to provide child care."

(ii) 45 CFR 46.111(a)(7): When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

OHRP finds that CHRCO IRB records for the above-referenced research demonstrate a failure of the IRB to obtain sufficient information regarding the privacy of research subjects and the confidentiality of data.

OHRP notes that the consent document makes the following statement: "Your participation, outside the group, is entirely confidential. We will make audiotapes of the group as well as a written report of the audiotape; however, all names will be kept confidential and excluded from the written report." However, the one and a half page document referenced above does not describe any specific provisions to protect the privacy of subjects and to maintain confidentiality of data.

(iii) 45 CFR 46.111(a)(1): Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes. 45 CFR 46.111(a)(2): 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.

OHRP noted in its July 7, 2005 letter to CHRCO that it appears that the IRB never received nor reviewed the focus group questions for this study. OHRP finds that the CHRCO IRB records for the above-referenced research demonstrate a failure of the IRB to obtain sufficient information regarding the risks and possible benefits of the research.

(iv) 45 CFR 46.111(a)(4): Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with 45 CFR 46.116. OHRP finds that CHRCO IRB records for the above-referenced research demonstrate a failure of the IRB to obtain sufficient information regarding the process for obtaining informed consent.

OHRP also finds that the informed consent document for the above-referenced research failed to include the following element required by HHS regulations at 45 CFR 46.116(a)(1): a statement that the study

involves research. The informed consent document is entitled "Consent to Participate in an Evaluation of the CVC using Focus Groups." Throughout the document, the research is referred to as an "evaluation" or an "evaluative project."

(b) "Search for Type I Diabetes Susceptibility Factors in a Continental Italian Population," Janelle Noble, principal investigator

OHRP finds that CHRCO IRB records for the above-referenced research demonstrate a failure of the IRB to obtain sufficient information to make the required findings in HHS regulations at 45 CFR 46.111.

The IRB file for this study does not contain a protocol or a CHRCO IRB application. It is unclear what materials the IRB Chair reviewed in order to grant expedited approval. The grant application to the American Diabetes Foundation contained in the file does not contain the specific information needed for the IRB Chair to appropriately consider the elements of the criteria for approval in HHS regulations at 45 CFR 46.111.

(c) "Pilot Study for Pulmonary Complications in Sickle Cell Disease," Carolyn Hoppe, principal investigator

OHRP finds that CHRCO IRB records for the above-referenced research demonstrate a failure of the IRB to obtain sufficient information to make the required findings in HHS regulations at 45 CFR 46.111.

In its August 15, 2005 letter, CHRCO stated that the samples were discarded blood samples with no identifiers given to the investigator. OHRP notes that if the samples were anonymized, and not merely coded, the activity may not meet the definition of human subjects research, as defined in 45 CFR 46.102. However, there is not enough information in the IRB file to be able to make this assessment. Research involving human subjects that is not exempt under HHS regulations at 45 CFR 46.101(b) may not be approved, either by a fully convened board or by expedited review, unless the requirements of HHS regulations at 45 CFR 46.111 are satisfied.

Corrective Actions: OHRP has reviewed the current CHRCO IRB "Application for Study Review" available on the CHRCO website. OHRP notes that the application solicits information, in pertinent part, about risks and benefits, recruitment, equitable selection of subjects, the informed consent process, and privacy and confidentiality. OHRP also notes that IRB minutes from year 2006 document discussions during full board meetings related to the required findings in HHS regulations at 45 CFR 46.111.

OHRP has determined that the corrective actions above adequately address OHRP's finding and are appropriate under the CHRCO FWA.

(2) It was alleged that the CHRCO IRB consistently fails to make and document required findings for waiver of informed consent, as required by HHS regulations at 45 CFR 46.116(d) when approving a waiver or alteration of some or all of the required elements of informed consent. OHRP finds that the following protocols lack documentation of required findings for waiver of informed consent: "The Role of Natural Killer Cell Immunoglobulin Receptors and Their HLA Ligands in Unrelated Blood and Marrow Transplants," Elizabeth Trachtenberg, principal investigator; "Search for Type I Diabetes Susceptibility Factors in a Continental Italian Population," Janelle Noble, principal investigator; and "Pilot Study for Pulmonary Complications in Sickle Cell Disease," Carolyn Hoppe, principal investigator.

CHRCO stated the following in its August 15, 2005 response:

> The failure of the IRB to make and document <sic> required finding for waiver of informed consent, as required by HHS regulations at 45 CFR 46.116(d) may represent an incomplete understanding of this requirement by the chair and the prior administrator. Each of the studies mentioned are "laboratory only" studies....involved the investigators receiving and analysis <sic> coded samples from preexisting specimens for which informed consent had been given to be collected and used in this type of research. The investigators had no access to protected health information or personnel <sic> identifiers at any time.

OHRP notes that the January 29, 2003 letter from the principal investigator to the IRB requesting expedited approval states: "The DNA samples are provided by my co-investigator....All sample collection and DNA preparation is performed in Italy with the approval of the Italian Ministry of Health. Purified DNA samples are encoded and shipped to my laboratory for genotyping.

OHRP notes that some research involving coded samples may be considered human subjects research. Please see the OHRP guidance document entitled "Guidance on Research Involving Coded Private Information or Biological Specimens," available on the OHRP website at http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.htm.

Corrective Actions: CHRCO stated the following in its August 15, 2005 response:

> A new procedure will now require that all convened and expedited protocols have either an informed consent or a documented waiver of informed consent based on the applicability of the criteria in 45 CFR 46.116(d). The Principal Investigator will complete a form that demonstrates that the protocol meets the criteria of 45 CFR 46.116(d). The IRB will then grant and document the waiver of informed consent as part of the review process.

OHRP has reviewed the form referenced above, entitled "Application for Waiver of Informed Consent," available on the CHRCO web site. OHRP has determined that the corrective actions above adequately address OHRP's finding and are appropriate under the CHRCO FWA.

(3) OHRP finds that the CHRCO IRB failed to conduct substantive and meaningful continuing review of research, as required by HHS regulations at 45 CFR 46.111. Protocols were voted on in blocks without individual discussion in many cases.

Corrective Actions: CHRCO stated the following in its August 15, 2005 response:

> As a result of this inquiry, we have reviewed and discussed the OHRP Guidance Document on Continuing Review as well as our own policies and procedures...We have instituted a more rigorous process whereby each continuing review is discussed with an emphasis on the points stressed in the Guidance letter, voted on individually after the opportunity for discussion. In addition the primary reviewers and panel members are to be provided the materials outlined in the Guidance letter...In addition, a new, more detailed, form for documenting continuing review is being developed and will be implemented...as well as updating our existing Policies and Procedures to reflect what is outlined in the Guidance document and the fact that we use a primary reviewer system for continuing renewals.

OHRP has reviewed the most recent version of the continuing review form, available on the CHRCO web site, entitled "Application for Continuing Review." In addition, OHRP has reviewed pertinent continuing review sections of IRB meeting minutes from February, August and November 2006.

OHRP has determined that the corrective actions above adequately address OHRP's finding and are appropriate under the CHRCO FWA.

(4) OHRP finds that the CHRCO IRB failed to conduct continuing review at least once per year, as required by HHS regulations at 45 CFR 46.109(e), for the following two protocols: "Evaluation of Project SPARK," Cheryl Zlotnick, principal investigator; "Baseline Study of Nosocomial RSV in NICU Patients," Richard Powers, principal investigator.

Corrective Action: CHRCO stated in its August 15, 2005 response that it had "initiated a review and organization of our files. At the time of each continuing review, the administrator and chair will more thoroughly review each file for completeness...All of our active studies are now in a more sophisticated database which should allow us to track continuing reviews..."

OHRP has determined that the corrective actions above adequately address OHRP's finding and are appropriate under the CHRCO FWA.

(5) It was alleged that CHRCO IRB records fail to include copies of all correspondence between the IRB and the investigators, as stipulated by 45 CFR 46.115(a)(4). OHRP is unable to substantiate this allegation.

(6) OHRP expressed concern in its letter dated July 7, 2005 that individuals without human subjects research expertise are listed as principal investigators for protocols. In its August 15, 2005 response, CHRCO indicated that there were a number of errors that occurred during data entry into the IRB database and that these errors have been corrected. In those cases, the principal investigator's name was correctly listed on the study documents and consent forms.

As a result of the above determinations, there should be no need for further involvement of OHRP in this matter. However, OHRP anticipates conducting a site visit to CHRCO within the next 12-24 months.

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,

Karena Cooper, J.D., M.S.W.
Division of Compliance Oversight

cc: Denyse Pettersson, IRB Administrator, CHRCO
Dr. John R. Waterson, IRB Chair, CHRCO
RADM Linda Tollefson, FDA
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