August 31, 2005

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RE: Defining and Handling Conflicts of Interests for Members of the Pediatric Central Institutional Review Board (PedCIRB)

Dear Dr. Christian:

The Office for Human Research Protections (OHRP) has carefully considered the information provided in the National Cancer Institute's (NCI) July 27, 2005 position paper, entitled "Central IRB Membership: Enrolling Subjects, Conflict of Interest and the Central IRB Initiative," as well as the many views expressed by the NCI staff, U.S. Food and Drug Administration staff, NCI PedCIRB members, advocates for pediatric cancer patients, and Children's Oncology Group (COG) investigators who met with OHRP staff on July 29, 2005.

Based on the information and views presented in the NCI position paper and during the July 29 meeting, OHRP has decided to clarify its initial thoughts regarding PedCIRB member conflicting interests in a manner that narrows the scope of what should be considered a conflicting interest for PedCIRB members who are also COG investigators. In particular, OHRP has decided that NCI's proposed criteria for defining conflicting interests for PedCIRB members who are also COG investigators would be acceptable if modified as described later in this letter. The remainder of this letter provides a summary of the pertinent regulatory provisions and an overview of how OHRP's deliberations on this issue have evolved to its current viewpoint.

Department of Health and Human Services (HHS) regulations for the protection of human subjects at 45 CFR 46.107(e) stipulate that no IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB. The purpose of this provision is to ensure that the IRB review of research is objective, unbiased, and independent. IRB members should be free of any conflicting interests that might alter their evaluation of and action on research undergoing IRB review. It is particularly important that IRB members be free of any conflicting interests that could hinder their deciding to disapprove research.

As you are aware, with respect to the provisions of HHS regulations at 45 CFR 46.107(e), in deliberating as to what constitutes a conflict for NCI PedCIRB members who are also COG investigators, OHRP initially expressed the following viewpoint:

> In general, when a COG investigator is serving as a member of the PedCIRB, OHRP would consider such a member to have a conflicting interest for a COG protocol undergoing initial or continuing review whenever that IRB member, given the scope of his or her clinical and research duties, has a reasonable expectation of enrolling and/or managing subjects on that oncology group protocol in the future, regardless of whether the IRB member serves on any oncology group committee related to the development or management of the protocol.

Furthermore, OHRP deemed the following two options for avoiding having COG investigators with conflicting interests participate as IRB members in the PedCIRB's review of research to be permissible under the HHS regulations at 45 CFR part 46:

> Option 1: When a COG investigator on the PedCIRB has a conflicting interest for a specific oncology group protocol because the member has a reasonable expectation that he/she would enroll subjects in the protocol in the future, the COG investigator would not serve as a PedCIRB member during the review of that protocol, but would participate as an expert consultant in accordance with HHS regulations at 45 CFR 46.107(f). The minutes of the central IRB meeting would reflect this change in status of the COG investigator, and the conflicted COG investigator would provide expert advice to the PedCIRB, but would not participate in the final deliberations or vote on the protocol.
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> Option 2: Instead of having a COG investigator whose status alternates between PedCIRB member and expert consultant to the PedCIRB during the course of a meeting (as would be the case for option 1), have a cadre of COG investigators who only serve as expert consultants to the PedCIRB for all protocols presented for review.

In response to OHRP's initial viewpoint, NCI staff and the PedCIRB members have asked OHRP to reconsider its viewpoint as stated above. In its July 27 position paper NCI argues that PedCIRB members who are also COG investigators would not have a conflicting interest for a particular protocol undergoing initial or continuing review when their participation in that protocol is limited to enrolling and managing subjects in the protocol. Under NCI's position, PedCIRB members who are also COG investigators would have a conflicting interest for a particular protocol undergoing initial or continuing review if they have an interest based on financial considerations, expected authorship of trial-related publications, academic advancement, enhancement of professional reputation, or increased institutional patient referrals. More specific examples of PedCIRB members who would be considered to have a conflicting interest for a particular protocol under the NCI position paper include the following:

> (1) A member who is the COG Principal Investigator (PI) at an institution who intends to participate in the protocol.

> (2) COG investigators who (a) designed and wrote the protocol; (b) have a prominent role in the COG disease committee submitting the protocol or the COG national study committee; or (c) will be involved in the analysis and/or publication of the data obtained under the protocol.

Based on the information and views presented in the NCI position paper and during the July 29 meeting referenced above, OHRP has decided that NCI's proposed criteria for defining conflicting interests for PedCIRB members who are also COG investigators would be acceptable under the applicable HHS regulations with the following additional modifications:

> With respect to a particular COG protocol undergoing review by the PedCIRB, a PedCIRB member who is a COG investigator has a conflicting interest if the COG investigator has either (a) identified a prospective subject for the protocol, or (b) enrolled a subject in the protocol.

OHRP's rationale for including these additional criteria for defining a conflicting interest for PedCIRB members who are also COG investigators is that they have an actual conflicting interest based on the following factors:

> (1) Once the COG investigator who is also a PedCIRB member seeks or obtains informed consent of subjects, or performs or directs research interventions and interactions with subjects, for a particular COG protocol, the COG investigator becomes an active investigator for that protocol.
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> (2) At the point that a PedCIRB member who is also a COG investigator identifies a particular patient as a prospective subject for a particular COG protocol undergoing review by the PedCIRB, the member becomes an advocate for and promoter of that protocol.

These two factors result in a conflicting interest under 45 CFR 46.107(e) that would limit the PedCIRB member's participation in initial or continuing review of the protocol as required by that section of the HHS regulations.

OHRP considered whether an actual conflicting interest exists for PedCIRB members who are also COG investigators even if they have not identified any patients who are prospective candidates for a particular COG protocol undergoing review by the PedCIRB nor enrolled a subject in the protocol. OHRP believes that it is reasonable to consider such circumstances as not rising to the level of an actual conflicting interest for the PedCIRB members who are also COG investigators, even if they have a reasonable expectation of enrolling and/or managing subjects in the future on a particular COG protocol undergoing review by the PedCIRB.

OHRP notes that NCI's proposed criteria for defining conflicting interests for PedCIRB members who are also COG investigators along with OHRP's additional modifications would be consistent with the current PedCIRB Conflict of Interest Policy appended to NCI's position paper.

OHRP notes that these conflict of interest considerations are not unique to the PedCIRB, but are relevant to any IRB that is reviewing COG protocols. OHRP also recognizes the value of the perspective that the public may have on OHRP's determinations in this matter. Therefore, OHRP intends to post this letter on its website and invite comments from members of the public. OHRP may revise its viewpoint on this matter further based upon comments received from the public.

OHRP appreciates the continuing commitment of NCI and the PedCIRB to the protection of human subjects. Please feel free to contact me if you have any questions regarding this matter.

Sincerely,

/s/

Bernard A. Schwetz, D.V.M., Ph.D.
Director
Office for Human Research Protections