

Central IRB Membership: Enrolling Subjects, Conflict of Interest and the Central IRB Initiative

When 45 CFR 46 was promulgated 30 years ago, the conduct of biomedical research differed dramatically from the contemporary practice of multi-institutional clinical trials. Federally-funded clinical trials were most often conducted at a single institution or among a handful of institutions; therefore, when the federal government created the regulatory scheme for human subject review, an institutionally-based approach was logical. Federal regulations specified that IRBs be “sufficiently qualified through the experience and expertise of its members ... to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects”.¹ During that same era, conflict of interest of Board members was considered so self-evident that the IRB regulations did not define “conflict of interest” for IRB members, stating only “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.”²

Today, however, a typical phase 3 cancer clinical trial is conducted at 50-500 sites, and the focus on investigator conflict of interest has intensified. New models of human subject protection have been developed³ which require reassessment of how investigator-Board member conflict of interest is defined and managed. In this context, the discussion below focuses on conflict of interest, specifically that of physician members who sit on a nationwide central IRB and who also have the potential to enroll patients on those same trials at their local institutions.

In 2001, the NCI piloted a central IRB (CIRB) for multi-institutional phase 3 adult clinical trials conducted by the NCI-supported cancer cooperative groups.⁴ A facilitated protocol review model, one of the options for central IRBs acceptable to OHRP, was established in which the CIRB conducts full board review and generates a review packet including the minutes of the CIRB meeting, the Board’s final comments on the protocol and an IRB application form for the protocol. The institutional IRB chair or IRB subcommittee utilizes the protocol application and review packet to conduct a subsequent brief review to address local issues related to conducting the clinical trial at the individual institution. If the local IRB chair has no institutional concerns and accepts the CIRB review, the CIRB becomes the IRB of record and the CIRB assumes responsibility for amendments, adverse events (AEs) (with the exception of AEs occurring at the local site which are reported to the local IRB to keep them alerted to local safety issues) and continuing reviews for the life of the protocol. In late 2004, NCI established a second CIRB to review phase 2, 3 and pilot pediatric protocols that also used the facilitated review model.

¹ 45 CFR 46.107(a)

² 45 CFR 46.107(e)

³ BRANY, MACRO, NCICIRB

⁴ Christian, M. C., et al. *N.Engl.J Med.*, 346: 1405-1408, 2002

July 27, 2005

As stated above, federal regulations and guidance do not explicitly define conflict of interest, thereby leaving IRBs, including the NCI CIRBs, to define conflict of interest for themselves. The CIRB conflict of interest policy states that CIRB Board members who are involved in the development, conduct or analysis of the trial under review or who have prominent roles in the disease committee submitting the trial are considered to have a conflict of interest and are recused from the protocol discussion and vote. With the advent of the Pediatric CIRB (PedCIRB), conflict of interest was revisited with OHRP and led to more specific direction. The most recent advice provided by OHRP requires Board members to recuse themselves from the review of trials on which they have a “reasonable expectation” to enroll patients during and after their PedCIRB tenure:

In general, when a member of one of the NCI-sponsored oncology groups is serving as a member of one of the NCI Central IRBs, OHRP would consider such a member to have a conflicting interest for an oncology group 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.⁵

The current review procedures adopted by the PedCIRB to comply with these terms are provided at the end of this document.

Following extensive discussions with PedCIRB members and ongoing discussions within CTEP/NCI, we take the position that PedCIRB members whose participation in the clinical trials process is limited to enrolling patients in a manner consistent with pediatric oncology clinical practice have no conflict of interest in reviewing trials. No benefits accrue to these members that would bias either their review of the trial or any subsequent decision to enroll a patient. Taking the position that PedCIRB members who enroll patients onto clinical trials are conflicted relegates practicing pediatric oncologists to a consulting role on the PedCIRB. In the short-term, this approach may not compromise the quality of PedCIRB reviews. However, in the long-term, this approach will make the recruitment and enthusiastic participation of pediatric oncology Board members more difficult. These are the very individuals “possessing the professional competence necessary to review specific research activities” as specified in federal regulations,⁶ and their diminished participation will compromise both the quality of PedCIRB reviews and the perception of the quality of the review by local IRBs. Inevitably, this perception of lack of expertise will slow or halt the affiliation of local IRBs with the CIRB and jeopardize the entire Initiative.

Prior to discussing specific issues related to conflict of interest for practicing pediatric oncologists who serve as PedCIRB members, it is necessary to first review how the

⁵ Email correspondence from OHRP to NCI-CTEP dated 04/04/05._____.

⁶ 45 CFR 46.107(a)

practice of pediatric oncology has evolved over the past four decades.⁷ Pediatric cancer specialists in North America have cooperatively designed and conducted sequential, randomized phase 3 clinical trials for over four decades in order to use evidence-based information to refine the treatment of children with cancer. The "state-of-the-art" treatment for a child with cancer derives from the best therapy identified in prior clinical trials and this best available treatment serves as the standard arm of subsequent phase 3 clinical trials.

The pediatric oncology community of physicians, other health care providers, and patient advocates generally accepts that it is appropriate to offer families of children with cancer the opportunity to participate in appropriately designed clinical trials, with families being free to accept or decline participation without penalty. This practice is deemed necessary because most current therapies are inadequate because of insufficient efficacy and/or excessive toxicity, and because well-designed clinical trials are required to identify more effective treatments. Implementation of this approach in an ethically acceptable manner requires multiple safeguards to ensure that the risks and benefits to research subjects remain in balance throughout the course of the clinical trial. Various groups share responsibility for this task, including the research team, government agencies with review responsibilities (e.g., NCI and FDA), Data and Safety Monitoring Boards, and IRBs. The close linkage in pediatric oncology between clinical practice and research requires acknowledgement of the tension between the practitioner's roles as a clinician and as an investigator. As an example, the Children's Oncology Group (COG) is addressing this tension by studying the informed consent process to clarify and to improve both the decision-making process that families encounter and the information provided by the pediatric oncology team.

The pediatric oncology model described above has important implications for discussions about conflict of interest for physician PedCIRB members. Because pediatric oncologists offer families participation in clinical trials as part of the clinical care process, the vast majority of such physicians eligible to serve on the PedCIRB would likely enroll patients onto clinical trials. Hence, it is critical to determine whether the tension that exists in this investigator-physician role rises to the level of conflict of interest for physician PedCIRB members.

Conflicts of interest are most commonly thought to occur when the investigator may be biased by financial gain as the secondary interest. In addition, other secondary gains may include authorship of trial-related publications, academic advancement, enhancement of professional reputation or increased institutional patient referrals. It can be argued that oncologists who serve on the PedCIRB who have a reasonable expectation of enrolling or managing subjects on PedCIRB reviewed protocol in the future do not fall into any of these four groups.

For at least the last 20 years, the large majority of children with cancer in the United States have been treated on or according to COG protocols. Virtually all physicians and

⁷ Anderson, B. D., Smith, M. A., Reaman, G. H., and Kodish, E. D. Re: Views of American oncologists about the purposes of clinical trials. *J Natl Cancer Inst*, 95: 630-631, 2003

July 27, 2005

health professionals caring for children diagnosed with cancer have some association with the COG. However, the large majority of these physicians and health professionals caring for these children have no direct involvement in the development or management of specific trials. (The existing PedCIRB conflict of interest policy excludes members of the PedCIRB who sit on COG study committees or data monitoring boards from participating in, or voting on, protocols with which they might be involved).⁸

PedCIRB members have no potential for financial gain related to the future patient enrollment of subjects on a clinical trial. Local institutions are reimbursed on a per study entry case basis by COG from an NCI grant. These funds are usually used to subsidize the increased institutional administrative salary burden for Clinical Research Associates required for COG study entry and data compliance. It is widely acknowledged that NCI's reimbursement for research costs, currently \$2,000 per patient, is far less than the actual costs incurred by institutions to participate in NCI-sponsored clinical trials. Institutions essentially contribute the balance of the research costs, making clinical trials participation a net loss rather than a financial benefit. The local disbursement of these funds is controlled by the COG institutional principal investigator (PI), not by the oncologist registering the patient on study. The existing PedCIRB conflict of interest policy excludes local institutional PIs from serving on the PedCIRB due to the distribution of per patient reimbursement for protocol accrual to the institution.

There is minimal likelihood for publication authorship, academic advancement, or enhanced professional reputation associated with Board member protocol review. Such academic benefits go to members of the COG national study committee or the COG disease committee. These persons are excluded from service on the PedCIRB by PedCIRB conflict of interest policies.

There is no likelihood for increased institutional patient referrals related to Board member review of a COG trial. The large majority of pediatric oncologists in the United States are COG members and already have access to COG clinical trials for their patients.

For the reasons cited above, we conclude that physician PedCIRB members whose participation in COG clinical trials is limited to offering protocol participation to families in a manner consistent with pediatric oncology clinical practice do not have a conflict of interest that would preclude them from reviewing COG clinical trials and, in fact, are performing a service both for child research subjects and for the cancer research community.

Proposed Policy for PedCIRB Members.

1. PedCIRB members are in conflict if they have a primary role in the oversight, design or conduct of the clinical trial or have a role in the analysis or management of the clinical trial data.
2. PedCIRB members whose participation in the clinical trials process is limited to enrolling patients in a manner consistent with pediatric oncology clinical practice do not have a conflict and may fully participate in reviewing clinical trials.

⁸ See end of this document for "Pediatric CIRB Conflict of Interest Policy and Procedure".

July 27, 2005

Summary:

CTEP believes that PedCIRB members who are practicing pediatric oncologists and who meet the PedCIRB's conflict of interest requirements can conduct the initial and ongoing review of COG clinical trials without conflict of interest. These Board members would not obtain financial, academic or institutional benefit from either participating in PedCIRB reviews or from offering enrollment onto a PedCIRB reviewed trial to potential research subjects as part of their clinical practice. Therefore, we conclude that physician PedCIRB members whose participation in COG clinical trials is limited to offering protocol participation to families in a manner consistent with pediatric oncology clinical practice do not have a conflict of interest that precludes them from fully participating in PedCIRB reviews of COG clinical trials.

The PedCIRB benefits from the full participation of practicing pediatric oncologists as Board members and from the pediatric oncology expertise and practical experience that they can share with the Board. Alternatives that relegate practicing pediatric oncologists to consulting roles on the PedCIRB, while not necessarily compromising quality of PedCIRB reviews in the short-term, will make the recruitment and enthusiastic participation of pediatric oncology Board members more difficult. The eventual result of these alternatives will be a perception of lack of expertise for PedCIRB reviews that will slow or halt the affiliation of local IRBs with the PedCIRB. As a primary purpose of the NCI CIRB Initiative is to improve the clinical, scientific and ethical expertise of protocol review, failure of the PedCIRB to achieve its goals will diminish research subjects protection and mean that children with cancer are less well served.

July 27, 2005

Background Information – Interim Operating Procedures for PedCIRB

The PedCIRB is currently operating in a manner consistent with the most recent advice provided by OHRP that requires Board members to recuse themselves from the review of trials on which they have a “reasonable expectation” to enroll patients during and after their PedCIRB tenure. A general outline of procedures relevant to implementation of this advice is provided below:

1. PedCIRB members may participate in the discussion of the protocol under review. Members who have identified a potential enrolling authority conflict of interest recuse themselves from the final deliberations and voting on the clinical protocols for which they have declared a potential conflict. While the potentially conflicted Board members do not participate or provide unsolicited input during the final deliberations or voting, they are available as a resource to the voting member body as needed until the final vote.
2. Board members, if they so choose, may define a specific tumor(s) for which the member will continue to enroll and manage patients as a clinical trial investigator at their local institution. These Board members will recuse themselves from the final deliberations and vote for any protocol concerning the designated tumor(s) for which they plan to participate as an investigator and will function as non-conflicted Board members for studies involving all other tumors.
3. The minutes of the PedCIRB meeting reflect traditionally defined conflicts of interest in addition to potentially enrolling authority conflicts for PedCIRB Board members for each protocol reviewed.

July 27, 2005



Pediatric CIRB Conflict of Interest Policy and Procedure

The purpose of this policy is to ensure that all deliberations of the NCI Pediatric Central IRB (the Board), affecting participants in research projects, are conducted and concluded by members whose overriding interest is the protection of those participants. At the same time, in furtherance of that protection, the policy is not intended to unnecessarily deny the Board the benefit of the expertise of any of its members in such deliberations.

To these ends, when it is determined that any member has an existing conflict of interest in any such project before the Board, that member shall be absent throughout the deliberations concerning that project and voting thereon, except when a majority of the members not so conflicted shall request that member's presence for the sole purpose of responding to questions. A member may deem herself/himself to possess a conflict of interest for any reason.

A conflict of interest may exist when:

A. A member or her/his immediate family member (significant other or dependent child) or a person in a direct supervisory or reporting relationship with the member has a primary role in the oversight, design or conduct of the project or has a role in the analysis or management of the data. This includes but is not limited to:

1. serving on a governing body of any significant supervisory committee, serving as a Chair of a currently active study, a Disease Committee, the Board of Directors, or a Data Monitoring Committee of the Cooperative Group, or of the Grantee Organization of the Cooperative Group that submitted the protocol under consideration;
2. being at the same institution as the protocol or project's Study Chair or Principal Investigator;
3. being the Cooperative Group Principal Investigator at an institution which intends to participate in the study/project/protocol under Board review.

B. A member or immediate family member has a financial interest of \$10,000 or more in any of the agents/devices/enterprises involved in the protocol under consideration (Ownership interests arising solely from investment in a company by a mutual, pension or other institutional investment fund over which the IRB member does not have control shall not be included as a conflict of interest or deemed such.).

C. A member has a proprietary interest in the research, such as a licensing agreement, copyright, patent or trademark.

D. A member or immediate family member within two years before the deliberations receives any compensation from any enterprise involved in the protocol under consideration.

E. A member has enrolling authority for any already identified patient she/he then intends to enroll in the protocol under consideration.

F. A member has potential to gain academic or career advancement based upon participation in the protocol.

G. A member has an interest (financial or non-financial) that the PCIRB believes conflicts with or biases his/her ability to objectively review a protocol

It is the responsibility of each member to disclose what she/he believes may constitute a conflict of interest as to a given project to the NCI PCIRB Coordinator as soon as that belief is harbored by the member, specifying the category of that conflict. If the member indicates, in the disclosure, uncertainty as to whether the disclosed relationship constitutes a conflict requiring her/his absence from the deliberations, that member shall disclose the pertinent facts of the questioned relationship. If there is time before the meeting, as should normally be the case, the question shall be submitted by the NCI PCIRB Coordinator to the PCIRB for a determination. All such determinations by the COI subcommittee for a given meeting shall be presented in writing to the Board no later than the beginning of such meeting

July 27, 2005

2

where they shall be subject to Board approval only if the subcommittee determination was not unanimous, or if appealed by the member alleged to be so conflicted. Conflict issues disclosed too late for subcommittee consideration shall be dealt with directly by the whole Board prior to any discussion of the project for which there is a potential conflict.

A copy of this policy shall be included in the members' packets for each meeting and the Chair shall call attention to the policy at the beginning of each meeting. An entry in each meeting's minutes will reflect adherence to this policy.