



June 3, 2009

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Darrell G. Kirch, M.D.
President and Chief Executive Officer

Subject: IRB Accountability RFI

Dear Ms. Kaneshiro:

The AAMC is a not-for-profit association representing all 130 accredited U.S. medical schools; nearly 400 major teaching hospitals and health systems, including 68 Department of Veterans Affairs medical centers; and nearly 90 academic and scientific societies. Our member medical schools and teaching hospitals collectively perform about 60 percent of all extramural research sponsored by the NIH.

The AAMC welcomes the opportunity to provide information and comments in response to OHRP's request dated March 5, 2009 of "whether OHRP should pursue a notice of proposed rulemaking (NPRM) to enable OHRP to hold institutional review boards (IRB) and the institutions or organizations operating the IRBs . . . (IORG) directly accountable for meeting certain regulatory requirements of the Department of Health and Human Services (HHS) regulations for the protection of human subjects."

As a co-sponsor and participant in the two national meetings on alternative, collaborative IRB models cited in OHRP's request, the AAMC has been engaged in a long-term effort to encourage the use of alternatives to local IRBs as a means to reduce substantial administrative burdens that have been identified in those meetings as well as by the Secretary's Advisory Committee on Human Research Programs (SACHRP). These burdens flow in part from the time and costs associated with duplicative IRB review for multi-site studies and also from inconsistent IRB review practices. If these burdens could be diminished or alleviated, it would be a substantial gain for HHS-funded research, without diminishing human subject protection.

A substantial barrier to the use of alternatives to local IRBs under appropriate circumstances was identified in both national meetings as OHRP's practice of only enforcing compliance with 45 CFR part 46 through the institutions that are engaged in human subjects research. This, as OHRP acknowledges in the ANPRM, "has been the case even in circumstances when the regulatory violation was directly related to the responsibilities of an external IRB that was designated on the engaged institution's assurance of compliance with OHRP." This enforcement pattern has been true, despite the fact that the regulations provide significant flexibility to

institutions to use a variety of cooperative review arrangements. AAMC, as one of the sponsors of the national meetings, believes that an expansion of the enforcement authority of OHRP to include IORGs may make institutions less reluctant to use alternatives to local IRBs, when circumstances warrant and human subjects protection is not diminished.

With respect to Section VI of the ANPRM, the AAMC appreciates OHRP's suggestions of which entities, as between the institution engaged in the research and/or the IRB/IORG, might be responsible for fulfilling various regulatory requirements. However, AAMC is concerned that if there is to be a grouping of responsibilities, the grouping should not be included within a regulatory framework. The level of detail associated with the categories offered in the ANPRM, if imbedded in regulation, could be seen as providing far too inflexible an allocation of responsibilities to accommodate the enormous variety of potential research projects and circumstances. Thus the AAMC urges OHRP not to designate regulatory categories, but to include language that confirms that institutions have flexibility in determining what responsibilities should reside where.

On the other hand, the research community needs to understand OHRP's view of issues that should be considered in the process of delegating responsibilities to an external IRB/IORG. As an alternative to regulation-based groupings, AAMC urges OHRP to indicate, in the form of guidance or points to consider, issues that institutions engaged in research might consider when formalizing a relationship on particular research projects with an IRB/IORG, without making any presumptions or mandates as to how responsibilities should be divided or covered. Whatever the decision on categories, in any division of responsibility, the allocation of responsibility should be clearly documented for each project.

Also, AAMC notes that in the second paragraph of Section VI, there is an ambiguous reference that should be corrected. The statement of concern is "OHRP considered whether there are any regulatory requirements that are inherently shared by both the IRB/IORG and the FWA-holding institution..." Because the IRB/IORG also can be an FWA-holding institution, AAMC urges OHRP to use the reference used elsewhere in the ANPRM, that is, "the institution engaged in the human subjects research", rather than the "FWA-holding institution".

In response to section VII, the AAMC's responses are as follows.

"1. Is there sufficient need for HHS to pursue a regulatory change to enable OHRP to hold IRBs and IORGs directly accountable for meeting certain requirements of the HHS regulations at 45 CFR part 46? Please explain your response."

NIH, OHRP, AAMC, and the American Society of Clinical Oncology (ASCO), spurred by interest expressed by SACHRP, sponsored two national meetings in 2005 and 2006 on alternative IRB models, with the Veterans Administration joining in sponsoring the 2006 meeting. The message from those meetings was clear. Prominent among the barriers identified

to the use of alternatives to local IRBs was regulatory liability. The Report of the 2006 conference summarizes the dilemma and the need for a regulatory solution:

“Participants believed that regulatory agencies could do much to encourage institutions to use external IRBs when appropriate. They recommended that regulatory agencies give clear signals that alternative forms of review are acceptable. In addition, because of concerns about the potential for regulatory liability resulting from the actions of an external IRB, participants asked HHS to revise its policies regarding the responsibility of institutions for all work conducted under their FWAs. They suggested that HHS consider policies similar to those of the FDA, which ties regulatory liability to the organization responsible for the alleged problem.”

Institutional legal counsels have long been concerned that their institutions would be held responsible by OHRP even where the fault lay with an external IRB. Such concern has heightened reluctance to use alternatives to local IRBs, even where circumstances have suggested that such use might be appropriate. The AAMC does not suggest this is the only barrier to the widespread use, under appropriate circumstances, of alternatives to local IRBs, but it has consistently been identified as one of the most prominent barriers, and it is amenable, in part, to the solution OHRP proposes in this ANPRM.

The increasing complexity of science and the emphasis on translational research and on converting discovery into the improvement of the health of the public often require multi-site clinical trials. Alternatives to local IRBs in such studies may provide a means for focused expertise, assessments of special kinds of risks, and they may therefore offer better protection for human subjects. Barriers to their use must be addressed and resolved.

“2. Would the proposed regulatory change reduce concerns about regulatory liability as a barrier to the use of external IRBs and contribute to an increase in collaborative IRB review arrangements?”

As indicated in the response to Question 1, above, the AAMC strongly believes that the proposed regulatory change would reduce concerns about regulatory liability as a barrier to the use of external IRBs and contribute to an increase in collaborative IRB arrangements. Such arrangements are a necessary part of the foundation for the science of today and tomorrow, so much of which will depend on collaborations across areas of science, institutions, and geographic boundaries. Our regulatory processes must maximize the protection of human subjects in research while at the same time minimizing obstacles to scientific collaboration.

“3. Are there other approaches and strategies that would decrease concern about regulatory liability and increase collaborative IRB review arrangements?”

There are additional approaches and strategies that could decrease concern about regulatory liability and increase collaborative IRB review arrangements. Clear expressions from funding agencies within HHS that collaborative IRB arrangements and alternatives to local IRB review

are strongly encouraged would enable the exploration and use of such alternatives under appropriate circumstances.

It should be noted that the proposed approach will not address private liability issues that continue to inhibit use of alternatives to local IRBs, but rather only regulatory issues. Nevertheless, the AAMC supports addressing the regulatory liability issue in the manner now being proposed by OHRP.

“4. If HHS were to issue a regulation that would enable OHRP to hold IRBs and IORGs directly accountable for meeting certain requirements of the HHS regulations at 45 CFR part 46, would this have the unintended effect of making institutions or IORGs less willing to have their IRBs designated as external IRBs on other institutions’ FWAs? If so, would there still be sufficient benefit for HHS to pursue a regulatory change to enable OHRP to hold IRBs and IORGs directly accountable for meeting certain requirements of the HHS regulations? Are there other possible unintended effects of the proposed regulatory change? Please explain your response.”

It is possible that the proposed regulatory change could have the unintended effect of making some institutions or IORGs less willing to have their IRBs designated as external IRBs on other institutions’ FWAs, but not highly likely. Institutions and IORGs already have contractual responsibilities to the institution on whose FWA they are included. The addition of a regulatory component to their liability adds a consideration, but not one that significantly alters ultimate responsibility. Furthermore, those external institutions and IORGs that already have the contractual responsibility should also have the regulatory responsibility.

There is another dimension that should be addressed, however, and it results from the confusing designations used by OHRP in the ANPRM itself. AAMC submits that an external IRB always is part of some institution, either an academic institution, a private corporation, or other legal entity. There must be some organizational form around the external IRB itself. It would have no legal status otherwise. AAMC assumes that OHRP intends by the phrase “IRB and IORG” to be referring to any external IRB, commercial, nonprofit consortium, another academic institution’s IRB, among other possible forms. But this phrase needs clarification. The purpose of any change should be to expand OHRP’s regulatory authority from the exclusive focus on the institution engaged in human subjects research to include the external organization, designated on the FWA of the institution engaged in the research, and its IRB. Better definition of what is intended by the phrase is essential.

“5. If HHS pursues a regulatory change to enable OHRP to hold IRBs and IORGs directly accountable for meeting certain requirements of the HHS regulations . . . what kinds of administrative actions would be appropriate...?”

The same kinds of actions that are appropriate for institutions engaged in human subjects research should be appropriate for IRB/IORGs.

“6. Three preliminary categories of regulatory requirements are proposed in the ANPRM, ones that may be unique to IRBs and IORGs, ones that may be unique to institutions engaged in human subjects research, and ones that may be fulfilled by either.

“6a. Are these categories appropriate? If not, what other categories should there be?”

As noted earlier in this letter, by means of guidance or “points to consider”, it would be helpful to understand OHRP’s view of issues for an institution engaged in research to consider in the process of delegating responsibilities to an external IRB/IORG. The AAMC urges OHRP not to designate regulatory categories, but to include language that confirms that institutions have flexibility in determining what responsibilities should reside where. Whatever OHRP’s decision on categories, in any division of responsibility, the allocation of responsibility should be clearly documented.

“6b. Is there a fourth category of responsibilities that are inherently shared...? If so, please provide examples....”

See the response to question 6a.

“6c. Are the regulatory provisions identified under each of the categories appropriate? If not, which . . . should be re-categorized, removed, or added?”

See the response to question 6a.

“6d. For institutions that have relied upon joint IRB review arrangements in the past, how have the regulatory requirements been divided or shared....”

The AAMC defers to individual institutions to provide the information requested.

“7. . . . [T]he IRB Authorization Agreement . . . is often used to clarify which entity will be responsible for carrying out these regulatory requirements.”

“7a. If a regulatory change . . . is pursued, should OHRP use the IRB Authorization Agreement or other forms of agreement . . . to inform its compliance oversight evaluations about which entity should be held responsible for fulfilling regulatory requirements that could be met by either an external IRB or the FWA-holding institution?”

The AAMC strongly believes that OHRP should use the IRB Authorization Agreement and any other form of agreement that exists between the FWA-holding institutions engaged in the research and the IORG to inform its oversight evaluations pertaining to its regulatory authority over the research in question.

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“7b. . . . [S]hould there be new provisions that require specific content or for other forms of agreements between external IRBs and FWA-holding institutions? If so, what types of content should be required?”

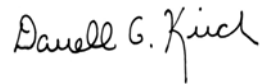
Flexibility is needed in these arrangements, but OHRP could offer examples on its website of agreements that have been used successfully.

“7c. . . . [S]hould the regulation describe which regulatory requirements would need to be met by external IRBs and which . . . would need to be met by institutions engaged in the research?”

Because of the need for flexibility in these arrangements to meet unique demands of particular research protocols and to accommodate different institutions' particular needs and resources as well as availability of appropriate expertise, the AAMC urges OHRP not to prescribe by regulatory requirement which requirements need to be met by external IRBs and which need to be met by the institution engaged in the research. The AAMC urges maximum flexibility at this stage in the encouragement of the use of collaborative, alternative models for IRB review.

The AAMC appreciates the opportunity to comment on this Advanced Notice of Proposed Rulemaking. Questions should be directed to Susan Ehringhaus, (202) 828-0543, sehringhaus@aamc.org or Irena Tartakovsky, (202) 862-6134, itartakovsky@aamc.org.

Sincerely,



Darrell G. Kirch, M.D.