



**Association of
American Medical Colleges**
2450 N Street, N.W., Washington, D.C. 20037-1127
T 202 828 0460 F 202 862 6161
www.aamc.org

Darrell G. Kirch, M.D.
President

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VIA ELECTRONIC MAIL: engagementohrp@hhs.gov

Engagement Guidance Comments
Glen Drew
Office for Human Research Protections
The Tower Building
1101 Wootton Parkway
Suite 200
Rockville, MD 20852

Dear Mr. Drew:

The Association of American Medical Colleges (AAMC) is a not-for-profit association whose membership includes 125 medical schools with accredited programs leading to the M.D. degree, 94 academic societies representing 105,000 faculty who conduct medical education and medical and health-related research including clinical trials, and approximately 400 teaching hospitals and health systems.

AAMC members conduct over 50% of the extramural research supported by the National Institutes of Health, and a substantial portion of the research supported by the Agency for Healthcare Research and Quality and the Department of Veterans Affairs Health System. Its members have a vital stake in the protection of human subjects involved in such research and in the ethics and effectiveness of clinical research. Indeed, the AAMC was instrumental in the creation of the Association for the Accreditation of Human Research Programs (AAHRPP).

AAMC is pleased to provide its comments on the Office of Human Research Protection's (OHRP) Draft Guidance on Engagement of Institutions in Human Subjects Research. We applaud OHRP's effort to clarify and refine the previous engagement guidance documents, and we strongly support the more nuanced precision that many of the draft provisions bring to the often difficult questions of when an institution involved in some aspect of non-exempt human subjects research is "engaged" in human subjects research.

OHRP asks in particular for comments on two examples provided in the draft Guidance of activities which would not result in an institution's being considered engaged in human subjects research. First, Example B(1) is a significant improvement over the current guidance and states

that an institution releasing identifiable private information is not the equivalent of obtaining identifiable private information, and thus, the institution is not engaged in an activity involving a human subject under 45 CFR 46. Though the Guidance does not purport to address the institution's obligations under HIPAA, questions will inevitably arise concerning the responsibilities of those IRBs that also serve as their institution's Privacy Board for HIPAA purposes. A clear statement that the Guidance has no effect on the definition of the institution's HIPAA responsibilities might be helpful.

The second example OHRP specifically asks about is Example B(7). This example is extremely helpful in its recognition of the frequent involvement of institutions not selected as research sites in the provision of trial-related services. AAMC strongly supports this more realistic and nuanced Example.

On the other hand, Example B(6) lacks clarity regarding the responsibilities of an institution operating a statistical center for a multinational clinical trial. The proposed guidance states that the institution's IRB "reviews and approves the component(s) of the research in which the institution is engaged." For a statistical center, the institution "must ensure that an IRB designated under its FWA reviews and approves the research activities related to the receipt and processing of the identifiable private information by the statistical center. In such a case, the IRB should ensure that the statistical center has sufficient mechanisms in place to adequately protect the privacy of subjects and maintain the confidentiality of the data."

Several possible interpretations of this latter sentence could be made:

- the IRB's review and approval of such research activities must consist of an assessment of the statistical center to determine if it has sufficient mechanisms in place to ensure that (1) the privacy of subjects and the confidentiality of data are adequately maintained, given the sensitivity of the data involved; (2) each collaborating institution holds an applicable OHRP-approved Assurance; (3) each protocol is reviewed and approved by the IRB at the collaborating institution prior to the enrollment of subjects; and (4) informed consent is obtained and documented from each subject in compliance with HHS regulations. This reflects the prior guidance from 1999.
- the IRB's review and approval of such research activities must consist of an assessment of the statistical center to determine if it has sufficient mechanisms in place to ensure that the privacy of subjects and the confidentiality of data are adequately maintained.
- the IRB must review, on a protocol-by-protocol basis, submissions from the statistical center that describe how the center staff will ensure that they have sufficient mechanisms in place to adequately protect the privacy of subjects and maintain the confidentiality of the data during their receipt and processing of identifiable private information.
- the IRB must review, on a protocol-by-protocol basis, submissions from the statistical center that describe how the center staff will ensure that they have sufficient mechanisms in place to confirm that (1) the privacy of subjects and the confidentiality of data are adequately

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maintained, given the sensitivity of the data involved; (2) each collaborating institution holds an applicable OHRP-approved Assurance; (3) each protocol is reviewed and approved by the IRB at the collaborating institution prior to the enrollment of subjects; and (4) informed consent is obtained and documented from each subject in compliance with HHS regulations.

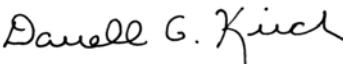
AAMC submits that the first interpretation reflects a more appropriate set of expectations for protecting research subjects than do any of the latter three. The second interpretation leaves uncertain what entity would help to oversee the human subject protection activities of collaborating institutions. The third and fourth interpretations place an undue burden on both the statistical center and the IRB overseeing its human subject protection activities by requiring a huge duplication of effort to ensure that subjects' privacy/confidentiality interests are protected.

Presumably the principles presented in the current draft guidance would apply to coordinating centers, as would these comments. For example, as described in the prior guidance (January 26, 1999) the IRB should determine and document that the coordinating center has sufficient mechanisms in place to ensure that (1) management, data analysis, and Data Safety and Monitoring (DSM) systems are adequate, given the nature of the research involved; (2) sample protocols and informed consent documents are developed and distributed to each collaborating institution; (3) each collaborating institution holds an applicable OHRP-approved Assurance; (4) each protocol is reviewed and approved by the IRB at the collaborating institution prior to the enrollment of subjects; (5) any substantive modification by the collaborating institution of sample consent information related to risks or alternative procedures is appropriately justified; and (6) informed consent is obtained from each subject in compliance with HHS regulations.

Finally, we endorse the comments submitted by the Council on Governmental Regulations and in particular its urging of OHRP to reconsider its position, reflected in Section IIIA(1) in which any prime recipient of an HHS award is engaged in human subjects research even in those cases where all the activities involving human subjects are carried out by another institution. AAMC strongly supports the responsibility for initial and continuing review being placed upon and remaining with the institution in the best position to monitor the project-related human subject activities. Requiring review by an institution that is not so positioned, even when it is the prime recipient, adds no greater protection for the subject, is contrary to the principle of reducing regulatory burden, and discourages the use of alternatives to local IRBs when such use would be optimal for protection of human subjects.

Thank you for the opportunity to comment on the draft Guidance.

Sincerely,


Darrell G. Kirch, M.D.