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May 24, 2005

**BY ELECTRONIC MAIL: EQFRN@osophs.dhhs.gov**

Ms. Gail Carter  
Division of Policy and Assurances  
Office for Human Research Protections  
1101 Wootton Parkway  
Suite 200, The Tower Building  
Rockville, MD 20852

**Re: Comments on the Protection of Human Subjects, Proposed Criteria for  
Determinations of Equivalent Protection**

Dear Ms. Carter:

I am writing on behalf of the Association of American Medical Colleges (AAMC) in response to the request for comments on criteria that have been recommended to the Office for Human Research Protections (hereinafter OHRP) for making determinations of whether procedures prescribed by institutions outside the United States afford protections that are at least equivalent to those provided in the Federal Policy for the Protection of Human Subjects (hereinafter referred to as the Common Rule). Comments were solicited by a Notice published in the Federal Register on March 25, 2005 (70 FR 15322).

The AAMC is a non-profit organization representing all 125 accredited U.S. medical schools, some 400 major teaching hospitals and health systems, and 94 academic and professional societies representing 109,000 faculty members. Much of the country's DHHS funded human subjects research is carried out under the auspices of AAMC member medical schools and teaching hospitals, and members of the AAMC's academic and professional societies often conduct it. The AAMC and its member institutions are committed to continuing to do their part to uphold the highest ethical standards in human subject research.

The increasing globalization of human subjects research, especially clinical trials research, has demonstrated the compelling need for the exercise of the regulatory authority conferred, in the case of DHHS, in 45 CFR 46.10(h) on department and agency heads to make determinations that procedures prescribed by institutions in foreign countries afford protections for human subjects that are at least equivalent to those provided in the Common Rule. An equally compelling need exists for OHRP to establish consistent criteria as a basis for its determinations, because OHRP has been delegated the authority of the Secretary of DHHS to make such determinations of equivalence.

The Working Group that was established in 2002 for proposing criteria for use by OHRP has recommended a framework for implementing this existing regulatory authority. It is this framework on which comments are now solicited.

The Working Group proposes approaching equivalent protections by identifying five separate steps in the evaluation of procedures of foreign institutions. These steps are an articulation of the specific protections in 45 CFR Part 46, Subpart A: assessment of the protections provided by the procedures of the institution [in the foreign country]; comparison of the protections provided by the institution's procedures with those provided by 45 CFR Part 46, Subpart A, and determination whether or not the institution's procedures provide at least equivalent protections; approval of the relevant department or agency head for the substitution of the institutional procedures; and assurance from the institution that the substituted procedures will be followed in the conduct of humans subjects research funded by HHS. The AAMC endorses this articulation of the steps to be used in making determinations of equivalence.

The Working Group then identifies seven specific protections afforded by 45CFR Part 46, Subpart A that it recommends as the principal dimensions for determination of equivalence. From this point forward, however, the recommended framework descends into a thicket of procedural necessities that obscures the seven specific protections and renders findings of equivalence virtually impossible unless the foreign institution has adopted substantially all of 45 CFR Part 46, Subpart A. Instead of acknowledging the existence of possible alternative systems that might be evaluated for equivalence, the Working Group recommendations appear to focus instead on demanding virtual identity of procedures, down to specific sections of 45 CFR Part 46, Subpart A. Though acknowledging that there could be "example procedures" that address in different ways one of the Working Group's seven specific protections and its associated 45 CFR Part 46, Subpart A authority, it is unclear how a foreign institution could meet the protections absent procedural detail that corresponds section by section to 45 CFR Part 46. Dwelling on this level of detail is an inappropriate focus for developing means by which the authority that currently exists to make determinations of equivalence may responsibly be exercised. Moreover, such a focus would necessarily require institution by institution assessment, which may result in further clogging OHRP's already burdened systems for responding to a variety of ethical imperatives.

The focus for developing means for equivalence determinations must remain on the general systems of protections and not become mired in specific procedural mechanisms. Otherwise, all that will be accomplished is an attempted export of the U.S. regulatory scheme (which is regarded by some merely as a floor). The purely procedural focus would also represent a failure to accommodate the increasing necessity for human subjects research, especially clinical trials, to be conducted internationally in a responsible, timely, and researcher/research institution-friendly manner. The focus must shift from a U.S.-centric definition of what constitutes responsible measures for addressing the seven specific protections to the protections themselves and alternative ways to achieve them. Only such a shift would enable consideration of other systems as potentially meeting the seven protections, assessment of the extent to which they already may effectively and adequately meet these protections, and perhaps most importantly, ready

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identification of those areas where the protections are not met, so as to enable steps to be taken to achieve equivalence. Otherwise, the framework provides no reliable assistance whatsoever to foreign institutions and is neither effective nor efficient in enabling determinations of equivalence, or in assessing compliance with objective standards.

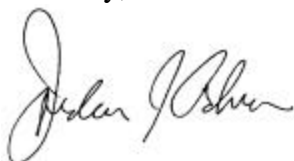
A serious omission in the Working Group's recommended framework for analysis is the failure to analyze established international systems of protection and ethical guidelines in terms of the seven protections it identified as the dimensions on which determinations of equivalence should be predicated. This deficiency could be addressed by explicitly looking to such systems, including, for example, the ICH Guidelines, the CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects, the Nuffield Council on Bioethics report, the International Guidelines for Ethical Review of Epidemiological Studies, and the World Health Organization's Good Clinical Practice Guidelines. It is these systems and guidelines that should be assessed against the seven identified protections, so that there will be reliable guidance, known in advance, for those seeking to conduct HHS funded research in foreign countries. It would be extremely useful if OHRP were to conduct pilot determinations of whether the seven identified protections were provided by established national systems from European countries or Australia. Do these systems provide equivalent protections or not, and, if not, what is lacking?

As to the additional specific questions posed by OHRP, the AAMC strongly urges that determinations of equivalent protections be made not on the basis of submissions by individual institutions but rather, where possible, on the basis of national or international procedural standards, that may then be relied upon by multiple institutions without repeated assessments. The AAMC recognizes that in some countries, standards and systems of protections are highly variable, and under such circumstances, countrywide determinations will be unworkable and must depend on institution-by-institution assessments.

Finally, the AAMC reiterates that the recommended seven criteria appropriately and adequately describe the protections provided to human subjects by existing Federal Policy. However, the linkage of current specific regulatory provisions as contributors to particular protections provided by the Federal Policy is not a useful approach for setting up a framework for evaluating different systems of protections. Standards of equivalence must be developed that allow other approaches to achieving protections, not just the particular provisions in 45 CFR 46, Subpart A. Determinations of equivalence should not be determinations of identity.

Thank you for considering the comments of the AAMC.

Sincerely,

A handwritten signature in black ink, appearing to read "Jordan J. Cohen". The signature is fluid and cursive, with the first name "Jordan" being the most prominent.

Jordan J. Cohen, M.D.  
President