Secretary's Advisory Committee on Human Research Protections
Charge, October 2024

Equivalent Protections and Procedural Requirements in International Research

The Office for Human Research Protections is requesting that SACHRP advise on the ethical principles that should be considered when making an equivalent protections determination under 45 CFR 46.101(h).

When nonexempt, human subjects research conducted or supported by HHS takes place outside of the United States, engaged institutions generally have to comply with 45 CFR 46 and its subparts, plus any applicable standards[1] in the host country.[2] Also, when a non-U.S. institution becomes engaged in research covered by 45 CFR 46, the non-U.S. institution needs to be covered by an OHRP-approved Federalwide assurance, and the IRB or similar ethics committee reviewing research covered by 45 CFR 46 for the non-U.S. institution has to comply with the 45 CFR 46 requirements applicable to IRBs, such as subpart E and the IRB membership requirements at §46.107. Differences between requirements in a host nation and in the Common Rule may create friction (*e.g.*, differences related to IRB membership). Since there has been an increased focus on U.S. research institutions that conduct international research collaborating with local communities, researchers, and organizations, it is expected that these tensions may become more common.

The HHS regulations at 45 CFR 46.101(h) recognize that "[w]hen research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth [in 45 CFR 46 and its subparts]". In these circumstances, the regulations allow a department or agency head to "approve the substitution of the foreign procedures in lieu of the procedural requirements provided [by 45 CFR 46 and its subparts]" after determining that "the procedures prescribed by the institution afford protections that are at least equivalent to those provided [by 45 CFR 46 and its subparts]".[3] Additionally, 45 CFR 46.101(i) permits a department or agency head to "waive the applicability of some or all of the provisions of this policy to specific research activities or classes of research activities… provided the alternative procedures to be followed are consistent with the principles of the Belmont Report."

Two groups have written about the issue of equivalent protections in reports both published in 2001. First, the National Bioethics Advisory Commission (NBAC), in its report "Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries"[4] suggested factors to use in making comparisons between protections provided by the HHS regulations and those provided in foreign countries. Second, the HHS Office of the Inspector General (OIG)'s report "The Globalization of Clinical Trials: A Growing Challenge in Protecting Human Subjects"[5] recommended establishing a means of making comparisons between protections provided by 45 CFR 46 and those provided in foreign countries.

Based on the recommendations from NBAC and OIG, HHS established an internal Equivalent Protections Working Group (EPWG) composed of representatives from several HHS agencies. The EPWG's 2003 report[6] suggested a framework for making equivalent protections determinations. On March 25, 2005, OHRP sought public comment on the EPWG report.[7] A summary of the comments is provided as Appendix A to this charge.

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[1] These may include laws, regulations, policies, guidelines, or other similar statements of ethical principles, whether mandatory or suggested, as these terms may have different meanings outside of the United States.
[2] *See*, 45 CFR 46.101(g), this policy does not affect any foreign laws or regulations that may otherwise be applicable and that provide additional protections to human subjects of research.
[3] Except when otherwise required by statute, Executive Order, or the department or agency head, notices of these actions as they occur will be published in the Federal Register or will be otherwise published as provided in department or agency procedures. 45 CFR 46.101(h).
[4] Available in two volumes at https://govinfo.library.unt.edu/nbac/clinical/Vol1.pdf, and https://govinfo.library.unt.edu/nbac/clinical/Vol2.pdf
[5] Available at https://oig.hhs.gov/documents/evaluation/2178/OEI-01-00-00190-Complete%20Report.pdf.
[6] Available at https://www.hhs.gov/ohrp/sites/default/files/epwgreport2003.pdf.
[7] Available in Pdf at https://www.gpo.gov/fdsys/pkg/FR-2005-03-25/pdf/05-5947.pdf, or in HTML at https://www.govinfo.gov/content/pkg/FR-2005-03-25/html/05-5947.htm.

However, a lot has changed since the publication of these documents 20 years ago. The regulations at 45 CFR 46, subpart A, were updated in 2017 (*i.e.*, "the 2018 Requirements"). The Covid 19 pandemic highlighted the importance of international cooperation in public health prevention and response. Additionally, research procedures that were not common back then have become more standard, such as decentralized clinical trials, cluster randomization, and studies that rely on big data, artificial intelligence, and other technological advances. There has also been much advancement in the related field of data protections. OHRP believes a fresh look at the issue of equivalent protections for HHS-supported or conducted research is justified.

With this in mind, OHRP seeks input from SACHRP regarding the following questions:

1. After implementation of the 2018 Requirements, what provisions in 45 CFR 46 and its subparts may create frictions because they differ from international standards such as the Declaration of Helsinki, and CIOMS? When answering this question, SACHRP may want to consider the requirements imposed by human research protections standards outside of the United States, such as, The Declaration of Helsinki, The Council for International Organizations of Medical Sciences (CIOMS) guidelines, The Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (a.k.a., The Oviedo Convention, which the European Union and other European countries rely on), and other similar international documents. OHRP provides these three as examples but will defer to SACHRP to identify which international standards they find it necessary to compare to 45 CFR 46 and its subparts (and not to other U.S. regulations or standards).

2. Are the frictions that these provisions create more prevalent in specific types of research (e.g., data science, behavioral research, etc.) or applicable to all human subjects research covered by 45 CFR 46?

3. What should be the ethical considerations when weighing whether international standards may provide equivalent protections?

4. What considerations should be assessed and what criteria should be applied to determine whether a specific provision of 45 CFR 46 should be waived or substituted for a specific research activity or class of research activities?

5. Taking all of the above into consideration, to what degree should HHS prioritize developing a path for equivalent protections determinations?

Appendix A: Summary of Public Comments on EPWG Report

Comments were received from sixteen respondents representing individuals, pharmaceutical manufacturers, advocacy organizations, trade associations, professional associations, federal agencies, a nonprofit research sponsor, and a foreign national government. The majority of comments favored the general approach recommended by the EPWG.

The questions in the March 25, 2005 Federal Register Notice, and the related comments included the following:

1. Is the recommended approach appropriate for implementing the authority under 45 CFR 46.101(h)?

Comments: Two-thirds of the nine respondents that addressed this question supported the EPWG's recommended approach, and several of those offered additional suggestions in response to this or other questions. One commenter noted the possible positive or negative effects on collaborations between U.S. research institutions and their international collaborators, but considered the use of protections rather than procedures as the basis for comparison to provide adequate flexibility. One commenter considered the EPWG's approach a reasonable start, but raised questions regarding how differing procedures would be treated, how investigator responsibilities would be addressed, and how research to which subparts B, C, and D of 45 CFR part 46 applied would be handled. One commenter endorsed the EPWG approach, but considered the described comparisons of procedures and protections to be excessively detailed. One commenter saw the framework for making EP determinations as a sound approach. That commenter also favored the in toto approach to comparisons.

One commenter found the EPWG approach insufficient because it considered only defined procedures independent of compliance with procedures, and focused on procedures rather than protections. The commenter saw the protections identified by the EPWG being rooted in procedure, rather than in principle, and consequently not fully embodying the principles laid out in the Belmont Report. The commenter claimed that the EPWG's protections omit entirely the principle of justice, and provide limited guidance for making decisions where the standard procedures for protecting human subjects may actually do harm. The commenter considered principles laid out in the Belmont Report to provide a more globally acceptable basis for evaluating equivalent protections.

One commenter considered the terms of assurance for the FWA to have already eliminated the requirement for compliance with 45 CFR part 46, thus eliminating the need for use of 45 CFR 46.101(h) authority. One commenter advocated expansion of the approach to include other international standards.

1.a. Is it preferable to make determinations of equivalent protections on the basis of submissions by individual institutions or on the basis of national or international procedural standards that may be relied upon by multiple institutions without repeated assessments?

Comments: Over three quarters of the nine commenters that addressed this question preferred EP determinations be made on the basis of national or international procedural standards. One commenter saw individual institutional standards as unable to provide a frame of reference for making EP determinations, and to create a risk of inter-reviewer variability. One commenter noted the efficiency of assessing national or international procedural standards that could be relied upon by institutions without repeated EP determinations needing to be made. Two commenters recognized that efficiency, but also noted that variations within some countries may require institution-by-institution assessments.

One commenter saw the variability of local conditions and compliance as a bar to EP determinations based on prescribed foreign procedures. One commenter urged that EP determinations be made at the

institutional, rather than national level because an institution without a formalized ethical structure is unlikely to be able to guarantee protections regardless of what is adopted at the national level.

2. Could an alternative approach provide equal or greater effectiveness and efficiency for implementation of this authority?

2.a. If so, what approach and why would effectiveness or efficiency be improved?

Comments: Nine commenters made recommendations ranging from closely aligned to the EPWG report to significantly different. One commenter recommended use of the Belmont Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research as the basis for making EP determinations, and saw the EPWG recommendations as echoing the principles of the Belmont Report. One commenter recommended the Declaration of Helsinki of the World Medical Association as the basis, but recognized that the Declaration of Helsinki addresses only medical research. Two commenters recommended adherence to the International Conference on Harmonization: Guideline for Good Clinical Practice (ICH-GCP) as the basis for making EP determinations.

One commenter recommended shifting the focus from a U.S.-centric definition of ways to achieve the protections to enable considerations of other systems. That commenter saw such a shift as facilitating assessment of the extent to which other systems do or do not provide the protections. That commenter also criticized the EPWG for not evaluating a number of international documents for whether the protections provided under those documents would adequately provide the EPWG identified protections and elaborating any ways in which the documents failed to provide those protections. One commenter recommended the establishment of a working group to do such an evaluation of the national and international documents currently listed on the FWA form for international institutions. One commenter recommended that HHS work in collaboration with the World Health Organization (WHO) to make a set of standards and mechanisms for measuring the procedural standards of the developing world. One commenter advocated performing a comparison of 45 CFR part 46, subpart A, with multiple international guidance documents. One commenter suggested giving the Secretary a way to determine where assurances are appropriate and where case-by-case consideration is essential.

3. Do the recommended criteria appropriately and adequately describe the protections provided to human subjects by the Federal Policy?

Comments: Five commenters agreed that the protections provided by the Federal Policy were appropriately and adequately described, and no commenters disagreed. One commenter remarked on the omission of the Belmont Report from the described framework. One commenter asserted that the EPWG recommendations also meet the spirit of ICH GCP. One commenter questioned how explicitly compatibility with 45 CFR part 46, subpart A provisions will be required before an EP determination is made.

3.a. Do the regulatory provisions the working group cited as contributing to particular protections provided by the Federal Policy relate directly to those protections?

Comments: Five commenters agreed that the cited provisions related directly to the described protections, and no commenters disagreed. One commenter saw the protections as only possible in a functional legal system where compliance and enforcement are likely. One commenter recommended including the requirements of the National Institutes of Health Office for Biotechnology Assessment (OBA) and the U.S. Food and Drug Administration (FDA).

4. Is the procedure recommended by the working group for seeking a finding of equivalent protections under 45 CFR 46.101(h) appropriate?

Comments: Five commenters supported the procedure and made recommendations for enhancement or implementation, while two commenters recommended different procedures. One commenter advocated ICH-GCP as an equivalent procedural standard. One commenter sought additional detail on how EP determinations would be made. One commenter endorsed the process but disagreed with what was perceived as the EPWG discounting of the investigator's role in the protections provided by 45 CFR part 46, subpart A. One commenter sought further clarification on procedures, particularly timelines to reduce delays in research projects, and suggested research sponsors as evaluators of equivalency, alone or in combination with foreign ethical review boards. One commenter sought clarification of the impact of HHS oversight on existing foreign ethical review systems and institutions.

One commenter advocated reliance on U.S. Department of State documents as foundations for identifying legal, social, and societal contexts where EP determinations are appropriate. One commenter considered the listing of other procedural standards on the international FWA form to have ended authority for implementing 45 CFR 46.101(h) provisions, and made it necessary to remove other procedural standards from the FWA form in order to make EP determinations.

A number of commenters addressed points beyond the specific questions posed by HHS in the March 25, 2005 notice. Representative comments include the following:

Informed consent
Comments: Two commenters noted that informed consent is a major issue in some foreign countries because the concept of informed consent as provided for under 45 CFR part 46, subpart A, may be different or absent in some countries. They expressed concern that the absence of informed consent in some foreign countries could impair the ability of HHS to make affirmative EP determinations for institutions in those countries. Another commenter stated that HHS should recognize the major cultural, economic, and political differences between the U.S. and developing countries and involve appropriate expertise in making EP determinations.

Collaboration
Comment: One commenter recommended that all partners collaborating on a research project be held to the same rules/procedural standards.

Comment: One commenter noted that institutions in the U.S. collaborating with foreign institutions may establish joint practices for the review and approval of collaborative human subjects research protocols. This will build stronger collaboration, improve IRB communication, and enhance IRBs' decision-making.

Education
Comments: Two commenters recommended that HHS engage in international and domestic education programs for investigators involved in international human subjects research activities to promote the importance of institutional responsibilities in international human subjects research, particularly for behavioral and social sciences research.

Vulnerable Populations
Comments: Several commenters requested clarification regarding how EP determinations would affect research involving pregnant women, fetuses, neonates, children, and prisoners (vulnerable populations). Another commenter noted that vulnerable or special populations should share in research participation and in the research results without inappropriately excluding or dissuading participation.

Review of Requests for EP Determinations
Comment: One commenter expressed concern that HHS will not have adequate resources to review in a timely manner requests for EP determinations from individual institutions and recommended that EP

determinations be limited to assessments of international procedural standards that can be used by multiple institutions.

Comment: One commenter recommended that procedures for making EP determinations include a "decision board" that would conduct the review process for making EP determination and how its review will be subject to public participation; the membership of the "decision board" should be clearly identified and include representatives of all stakeholders.

Implementation Issues

Comment: One commenter asserted that it is impossible to have a standardized policy that incorporates so many foreign countries and all the procedures covered in 45 CFR part 46.

Comments: One commenter recommended that HHS work closely with organizations such as the WHO and international countries to examine the approaches for protecting human subjects that have been accepted and used without revamping what is already in place and without starting anew. Another commenter recommended that HHS consider working with the WHO to participate in pilot studies in developing countries to better understand human subject protection in those countries and the local politics, culture, and economics before to initiating or implementing any new policies or requirements related to EP determinations.

Comment: One commenter advised HHS not to assume that foreign or developing countries are totally ignorant of protecting their human subjects.

Comments: One commenter suggested that an assurance mechanism between the United States and foreign/developing countries would be the best instrument to formalize an agreement for countries to comply with certain conditions attached to United States Federal research funding. Another commenter recommended that when making EP determinations, HHS place emphasis on the responsibility and accountability of the research institution in a foreign country, as well as on the principal investigator, for providing equivalent protections.

Comment: One commenter stated that it is important for OHRP to understand that the procedures normally followed in foreign institutions may be different from those required under 45 CFR part 46, yet are consistent.

Comment: One commenter recommended that foreign developing countries not be presented with complex and lengthy U.S. policies and procedures, but instead be presented with very straight forward, simple procedures and policies. That commenter suggested that after the policy for making EP determinations is developed and implemented by HHS, a monitoring committee comprised of international and domestic representatives be formed to develop on an annual basis recommendations for improving the HHS policy.

Comment: One commenter stated that the primary basis and goal of the specific accountability procedures for the provision of equivalent protections is the accountability of the research institution for establishing the expectation of ethical conduct for the welfare and rights of research subjects; therefore, the equivalent protections of human subjects in research are achieved as much through the proper implementation of institutional standard practices and procedures, as through the application of ethical principles in a formal institutional ethics committee review. That commenter noted further that the major responsibility for protecting human subjects is that of the institution followed by review by the institutional ethics committee. Another commenter stated that EP determinations should first be based on the principles contained within the procedural terms ascribed to by the institution and then the institution's individual written policies and procedures for the protections of human subjects.

Comment: Several commenters encouraged HHS to recognize some procedures in foreign countries may provide protections superior to those provided by under the Federal Policy. One commenter noted that the

EPWG proposal to evaluate foreign research protections in toto and not always an exact point-for-point matching of every element of the Federal Policy affords flexibility to give credit and praise to international systems that exceed U.S. standards, even in elements for which the Federal Policy may be silent or less protective.

Comment: One commenter urged HHS to be sensitive to the potential consequences and effects of a negative EP determination and to avoid decisions that could inhibit useful progress in research. That commenter noted that the immediate consequences of a negative EP determination may be to jeopardize U.S. funding, impede clinical trial progress, or alter medical product development plans. That commenter also acknowledged that when serious protection deficiencies are recorded, these may be appropriate results.

Comment: One commenter noted that institutions conducting research in the foreign country for which an affirmative EP determination was made would follow the procedures determined to provide equivalent protections and asked whether U.S. investigators working in that country could follow the foreign procedures.

Comment: One commenter stated that a linkage of specific regulatory provisions as contributors to particular protections is not a useful approach for evaluating different systems of protections and standards of equivalence must allow other approaches to achieving protections, not just the particular provisions in 45 CFR part 46, subpart A.

Comment: One commenter noted that experience demonstrates that a procedure may facilitate protection, but does not by itself provide protection; for example, recordkeeping may protect an institution and allow compliance audits by OHRP, but not protect research
subjects, and that context may affect the locus of responsibility for protecting them.

Comment: One commenter stated that the EPWG recommendations demonstrate an intent to eliminate U.S. ethical review of studies conducted at foreign sites in favor of foreign jurisdiction.

Accreditation
Comment: One commenter asserted that a simple and affordable accreditation process would be needed before HHS could use the EPWG suggestion of reliance on accreditation as an indicator of equivalent protections.

Composition of EPWG
Comment: One commenter observed that the EPWG membership was exclusively American and urged that individuals from the international community who are involved in the conduct of HHS-supported research be included in discussions regarding the process for making EP determinations.