Report of the Equivalent Protections Working Group

Department of Health and Human Services

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Submitted to

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INTRODUCTION

In 2001, the National Bioethics Advisory Commission (NBAC) issued a report entitled Ethical and Policy Issues in International Clinical Trials in Developing Countries [1]. During the preparation of the report, the commissioners heard from U.S. and foreign researchers who had encountered difficulties and frustrations in trying to adhere to the Common Rule requirements in their research in other countries. The process of negotiating institutional assurances and the detailed procedural requirements of research ethics review, in particular, were seen by some as tedious and of dubious value for the protection of human subjects. [1, pp. 78-80] Some researchers expressed a preference for the development of international standards as a way of maintaining the ethical commitments in the U.S. regulations but avoiding the perception that the United States regulations are being "imposed" on other countries [1, p. 86] In response, NBAC recommended that "the U.S. government should identify a set of procedural criteria and a process for determining whether the human participants protection system of a host country or a particular host country institution has achieved all the substantive ethical protections" that the NBAC report described. [1, p. 89]

In September 2001, close on the heels of the NBAC report, the Office of Inspector General of the Department of Health and Human Services (OIG) published a report entitled: "The Globalization of Clinical Trials: A Growing Challenge in Protecting Human Subjects." [2] The report focused primarily on the Food and Drug Administration's (FDA) approach to assuring human subject protections in the clinical trials that are the source of data for drug licensing applications in the United States. The report highlighted the dramatic increase in foreign research activity over the past decade in countries with limited experience in the conduct of clinical trials, and the challenge this presents for assuring the same level of human subject protections as in domestic trials.

In addition, the OIG report recommended that the Office for Human Research Protections (OHRP) advocate for the development of a voluntary accreditation system for human research subject protection programs, and exert leadership in developing strategies to ensure that adequate human subject protections are afforded for non-U.S. clinical trials regardless of the source of U.S. funding for the trials. The Report then states:

> "…it could be particularly helpful for the Office for Human Research Protections to address how the Department can better assess whether other nations' laws and practices afford equivalent protections to those that apply to human subjects participating in clinical trials in the U.S. We recognize the sensitivities and complexities associated with such guidance, but the matter appears to warrant serious consideration." [2, p. 21]

The NBAC and OIG reports also spurred Congressional interest in the conduct of international research in general, and in equivalent protections specifically. A bill in the 107th Congress would have required that the Director of OHRP to determine and publish

a list of those foreign countries in which protections for human research participants are substantially equivalent to those of the United States. [3]

BACKGROUND ON EQUIVALENT PROTECTIONS

To our knowledge, there have been 3 previous discussions of equivalent protections in the literature. First, is the existing United States Agency for International Development (USAID) Equivalent Protections Policy [4]. Second, is the paper entitled "The Challenge of Equivalent Protection" commissioned by NBAC and written by Prof. Bernard Dickens [5]. And the third is the discussion in the NBAC report itself [6]. We have drawn from these sources for insights to shape our deliberations and proposals.

The USAID policy for EP has three main features. First, the policy identifies the "three pillars" of human subject protection as (1) Review by a properly constituted ethical committee or Institutional Review Board (IRB); (2) A meaningful assessment of risk/benefit by the IRB; and (3) A meaningful informed consent procedure (USAID EP Policy, p. 2). It then goes on to say that "(s)ubstantive application of the "three pillars" should generally satisfy (the) requirement" of providing protection that is at least equivalent to the Common Rule requirements. [4]

Second, the USAID EP Policy states that "research supported through or adhering to the standards established by United Nations agencies is considered to qualify as affording such "at least equivalent" protection." And third, the policy states that "(i)n assessing equivalency, the general concept should be whether protection under the system is for all practical purposes the same when viewed *in toto* and not whether any specific component (e.g., the precise make-up of the IRB equivalent (sic)) is identical." [4]

In his background paper for NBAC, Bernard Dickens points out that whereas the U.S. federal regulations are largely procedural in nature, 45 CFR § 46.101(h) cites the Declaration of Helsinki as the type of guideline that might satisfy the requirements of equivalent protections, even though it is, in Dickens words, "underdeveloped procedurally". [5, p. A-1 – A18] Dickens' conclusion is that "equivalence addresses substantive principles of ethical conduct of research with human subjects, and not only the process of review itself." [5, p. A3] He goes on to examine how these substantive principles might be satisfied through competent research ethics review, using procedures that differ from those provided in the U.S. federal regulations. Dickens also examines some of the legal implications of equivalent protections and concludes by suggesting that further guidance in international research ethics may not be desirable, since a great deal exists and further guidance may give rise to more confusion rather than clarification, though he believes that improved ethics review capacity and institutional commitment are clearly critical to the effective application of any equivalent protections policy by the U.S.

The NBAC report favors the *in toto* approach proposed by USAID, but suggests that a more specific set of substantive protections must be met while conducting the overall

assessment. These include: (a) prior review of research by an ethics review committee; (b) minimization of risk to research participants; (c) risks of harm that are reasonable in relation to potential benefits; (d) adequate care of and compensation to participants for injuries directly sustained during research; (e) equal regard for all participants; and (f) equitable distribution of the burdens and benefits of research [6, pp. 85-89]. These criteria, and the "three pillars" approach proposed by USAID, focus predominantly on the types of judgment that IRBs should arrive at in the course of their review of research proposals and on-going review.

A FRAMEWORK FOR THE IMPLEMENTATION OF EQUIVALENT PROTECTIONS

Since their inception, the regulations contained in Title 45 of the Code of Federal Regulations (CFR) part 46 subpart A (45 CFR 46), governing the protection of human subjects of biomedical and behavioral research in the United States, have included a provision that would allow the head of an authorized U.S. agency to determine whether the procedures adopted by a research institution in a foreign country provide protections for human subjects that are at least equivalent to those provided by the U.S. regulations. 45 CFR 46 deals with the protection of human subjects in research, and is the focus of our analysis in this report. Three of its provisions are directly relevant to equivalent protections. The first makes it clear that the policy applies to "research conducted, supported, or otherwise subject to regulation by the Federal Government outside the United States." (45 CFR § 46.101(a)). The second reference emphasizes that the policy "does not affect any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research." (45 CFR § 46.101(g)). And finally,

> "When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries may differ from those set forth in this policy. [An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly (sic) Declaration (Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human subjects is internationally recognized.] In these circumstances, if a Department or Agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the Department or Agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy…" (45 CFR § 46.101(h)).

Though brief, this section provides an orientation to equivalent protections' critical challenges. The regulation is concerned with: (a) procedures normally followed in foreign institutions; (b) that may differ from the procedures described in 45 CFR 46 (but that may be consistent with guidelines issued either by sovereign states or by an organization

whose function for the protection of human subjects is internationally recognized); (c) if these procedures can also be demonstrated to afford protections that are at least equivalent to those provided by 45 CFR 46; then (d) the relevant Department or agency head may substitute the foreign procedures in lieu of the procedural requirements of 45 CFR 46.

This summary suggests a framework by which criteria may be developed for determinations of equivalent protections. The framework has 5 main elements, the first 4 of which roughly correspond to separate steps in the process of determining equivalence (we have attempted to address the first step in this report), whereas the fifth is a separate step and does not factor into the account of how equivalence should be determined:

Steps in determining equivalence

1. Articulation of the specific protections embodied in 45 CFR 46;
2. Assessment of the protections provided by the institution's procedures;
3. Comparison of the protections provided by the institution's procedures with those provided by 45 CFR 46 and determination whether or not the institution's procedures provide at least equivalent protections;
4. Approval by the relevant department or agency head for the substitution of the institutional procedures in lieu of the procedures of 45 CFR 46;

Mechanism of assurance with OHRP

5. Assurance from the institution that the substituted procedures will be followed in the conduct of Department of Health and Human Services funded[1] human subjects research. The assurance will be completed and filed with OHRP

1. Articulation of the protections embodied in 45 CFR 46

45 CFR 46 lays out, in considerable detail, expectations about how institutions conducting research involving human subjects must organize and conduct the initial and on-going ethical review of human subjects research and provides specific guidance about particular aspects of this review, such as informed consent. The policy is not explicit about what it means by "protections" or, therefore, about what specific protections it affords. But since implementing the equivalent protections regulation would require comparison of the *protections* afforded by the procedures, and not simply the procedures themselves, any comparative exercise must begin with an account of the protections afforded by 45 CFR 46.

The concept of "protections" in research ethics has been shaped largely by the sobering history of abuses of human beings conducted under the aegis of "research". Although much has been made about the exploitation of vulnerable subjects through the history of research ethics it is less often acknowledged that most of the ethical violations have occurred within recognized research institutions. What 45 CFR 46 aims to establish are

[1] The current assurance process employed by OHRP permits institutions to decide whether the assurance covers only DHHS funded research, or is extended to all human subjects research conducted within the instutition.

approaches to reducing the likelihood of research-related harms to individual research subjects through appropriate vigilance and mechanisms to ensure high standards of institutional accountability. The policy focuses squarely on the mechanisms of accountability among the principal actors in human research protection: the institution in which, or through which, the research is being conducted; the IRB or Research Ethics Committee; and the Agency or Department Head with regulatory authority for research conducted with U.S. Public funds.

Although individual investigators have the primary moral responsibility for protecting the rights and welfare of human subjects, it is critical for any assessment of equivalent protections that 45 CFR 46 is not read as a framework of ethical guidance for investigators in the tradition of the Declaration of Helsinki or the CIOMS Guidelines. Those guidelines provide guidance and rationales for why certain research practices should be considered ethically acceptable and others not. 45 CFR 46, on the other hand, is the procedural implementation of the principles of respect for persons, beneficence, and justice described in the 1979 Belmont Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research [7]. As such it deals with procedures rather than the ethical basis of those procedures, and focuses on the institutional context by addressing the underlying conditions that are thought to be conducive to the overall protection of the rights and welfare of human subjects. The policy presumes that investigators will be prone to fewer errors in judgment, and subject to greater safeguards against neglect and willfully unethical behavior, in institutions that establish strong expectations of ethical conduct, backed by well-functioning mechanisms of oversight and accountability.

To clarify the scope of the equivalent protections provision, we have attempted a careful characterization of what protections we believe may be reasonably inferred from the content of 45 CFR 46. (see Table 1—Framework for equivalent protections). Two general conclusions may be drawn from this analysis: (1) that the primary focus of the policy is the accountability of the research institution for the welfare and rights of research subjects; and (2) that the overarching goal of the specific accountability mechanisms and procedures described in the policy is to establish expectations of ethical conduct within the research institution. Our analysis also suggests, therefore, that the protection of the welfare and rights of human subjects of research is achieved as much through the proper promotion and conscientious execution of standard practices and procedures within the institution, as through competent reasoned application of ethical principles in research ethics review. It also requires that three main levels of responsibility are recognized and met: (a) responsibilities of the institution; (b) responsibilities of the IRB; and (c) discretion on the part of the appropriate U.S. Department or Agency head to take action, where necessary, to ensure that the responsibilities are appropriately exercised (though this is not included in Table 1, since the discretion exists independent of the determinations of equivalent protections). Some responsibilities, such as ensuring the appropriate authority of the IRB, are restricted to one level, whereas others, such as continued oversight and monitoring, are distributed across all levels. Although the policy assumes that research investigators are critical

actors in the protection of human subjects, it does not explicitly address the full range of their responsibilities.

The USAID policy on equivalent protections introduced the idea of an *in toto* assessment applied to an institution's entire set of procedures. The NBAC report endorsed this strategy, though it offered a different set of substantive protections than those offered by USAID. Although we also see a need for an *in toto* assessment, we propose to employ it in yet another way. Specifically, we believe that the protections embodied in 45 CFR 46, and described above, generally represent broad and complex aims, each of which might be satisfied in a variety of different ways through a variety of procedures. Since we believe that the achievement of each of the listed protections should be considered necessary to ensure the ethical acceptability of human subjects research, we propose that the proper application of the *in toto* assessment is *within* each of these specific protections. For example, there has been considerable criticism about the 45 CFR 46 requirements related to written informed consent, particularly in some developing country settings in which signing a document may be a profound and intimidating experience. If a foreign country institution adopts procedures that require the Research Ethics Committee to exercise discretion in the appropriate utilization of signed informed consent, due to prevailing cultural conditions related to the social significance of signatures and the threat that signing an official document might present, an *in toto* assessment of the protection from inadequate disclosure and non-voluntary participation might conclude that the procedures and provisions related to informed consent that permit this discretion were adequate and culturally appropriate, as long as the other relevant procedures were deemed to give rise to sufficient protection of voluntariness and adequate disclosure. In this way, the protection itself remains necessary, but the specific ways in which it is satisfied is afforded reasonable latitude in decisions by OHRP.

In the following sections we briefly outline the responsibilities at each of these levels, based on our analysis of 45 CFR 46. Throughout these sections we have indicated in italicized text the implied protections and the mechanisms by which they are achieved. These are organized and presented in Table 1, which summarizes the protections, the 45 CFR 46 provisions, and some examples of procedures that might contribute to the specific protections, based on the provisions of 45 CFR 46.

Institutional Responsibility

As noted above, the ultimate responsibility for protecting the rights and welfare of human subjects under 45 CFR 46 falls to the institutions under whose auspices the research is conducted. Thus 45 CFR 46 elaborates procedures that may be thought of as providing broad protections for human subjects by ***establishing expectations of ethical conduct*** within the institution and by promoting standards of ***due diligence*** in the review and continued oversight of research. Under 45 CFR 46, institutions must give IRBs ***adequate institutional authority*** to ensure that they can conduct ***independent review***.

IRB Responsibility

The IRB is a legislatively mandated mechanism (in the United States) for institutions to ensure that research conducted under their responsibility receives review of the appropriate ***quality and comprehensiveness***. The policy may be thought of as providing "protections" from ***biased decision-making*** and ***arbitrary decisions***. Such decisions run the risk that interests other than the rights and welfare of human subjects may be given precedence and might adversely affect the risk profile of any given study. Thus IRBs must protect against ***unnecessary*** and/or ***unjustified risk***, which could undermine the ***informed and voluntary participation*** of research subjects, which the policy aims to protect through an elaborate set of procedural requirements. Institutions are also responsible for the ***continued oversight and monitoring*** of research activities. Although 45 CFR 46 is less explicit about the procedural requirements of continued oversight this is clearly an issue that falls within the purview of the IRB, but also requires shared responsibility throughout the research process.

Investigators' Responsibility

The bulk of the procedures outlined in 45 CFR 46 establish responsibilities of institutions and their IRBs. However, there are several places in which the policy also suggests responsibilities of investigators, namely in ensuring the ***informed and voluntary participation*** of research subjects, in the ***continued oversight and monitoring*** of the research, and in the on-going protection of the privacy of research subjects, which we have subsumed under the more general protection from unnecessary and/or unjustified risk. Since the responsibilities of investigators are not the main thrust of 45 CFR 46 we have chosen to incorporate these specific responsibilities with the substantive requirements of IRB review, rather than in a separate section for investigators. Rather than undermining the importance of the role of investigators in protecting human subjects, we believe this helps to present a clearer account of the framing of 45 CFR 46 and the focus of its specific protections.

Protections Embodied in 45 CFR 46

Institution
Establish norms of ethical conduct and due diligence in review and performance of research within the institution

Ensure adequate authority and independence of the IRB/Research Ethics Committee

IRB
Protect against biased and arbitrary decisions in research ethics review

Ensure sufficient quality and comprehensiveness of research ethics review

Ensure research ethics review and oversight are commensurate with risks to research subjects and vulnerability of the study population

Protect against unnecessary or unjustified risk throughout the course of the study (includes responsibilities of investigator(s))

Ensure voluntary participation after adequate disclosure of information related to the study (includes responsibilities of investigator(s))

Our attempt to articulate the specific protections embodied in 45 CFR 46, and the specific procedures they follow from, is intended to focus the analyses that will be required to determine the equivalency of foreign institutions' protections (and by extension the acceptability of the institutions' procedures). This framework should also offer institutions, and other guidance-setting bodies, a clear set of aims as they develop and refine their research protection programs. We would also expect that the framework would be useful to OHRP as it develops a process whereby institutions seek equivalent protections status.

2. Assessment of the protections provided by the institution's procedures

Table 1 provides a framework for identifying potential differences in protections between the practices normally followed at an institution seeking a finding of equivalent protections and the procedures described in 45 CFR 46. In the table the specific procedures described in 45 CFR 46 have been matched with the protections they are thought to provide. These protections have been inferred by us from our analysis of the regulations. An institution could similarly match its own procedures with the protections listed in Table 1 as part of its demonstration that they provide equivalent protections to those afforded by 45 CFR 46. Table 1 also provides examples of procedures that serve each of the protections, based on the language of 45 CFR 46. These are provided for illustrative purposes, not as a definitive set of criteria for equivalent protections.

In the case of an institution that has adopted guidelines issued by an organization whose function for the protection of human subjects is internationally recognized, a similar process may be employed to identify and articulate the protections. For institutions in countries with national laws or guidelines that are mandatory for research institutions in receipt of government support, or that may otherwise be adopted voluntarily, a single process of evaluation and approval by OHRP may satisfy this step in the determination of equivalent protections. In this case, national guidelines also offer additional evidence that procedures are, in fact, normally followed within an institution (an issue that we describe in greater detail below), since the assurance entered into with OHRP is bolstered by the institution's domestic requirements.

3. Comparison and determination of equivalence with protections in 45 CFR 46

It is beyond our scope to foresee all of the possible procedures that might be adopted by institutions for the protection of human subjects throughout the world. As a result, a

comprehensive, single list of institutional procedures that will satisfy the requirements of equivalent protections is neither feasible, nor in keeping with the charge of the regulation, which is to compare the protections offered by the procedures, not the procedures themselves.

Determining whether a given set of procedures does, in fact, give rise to the intended protections lies beyond the immediate requirements of equivalent protections, though the policy is clearly intended to detect systemic failures to protect human subjects through the provisions related to oversight and enforcement. The likelihood that protections will be achieved in fact is a function of the institution's commitment (among other things) and is embodied in the process of assurance, described below under section 5.

It is important to acknowledge, in the domestic application of 45 CFR 46, that we know relatively little about how uniformly its procedures are applied by U.S. institutions, nor whether, or to what extent, the intended protections are achieved on a routine basis in the United States. Empirical studies of informed consent in research in the United States, for example, suggest that the procedural requirements of 45 CFR 46 do not, in themselves, ensure that research subjects are uniformly knowledgeable and voluntary in their consent to participate in research [8]. Rather than offering license and a specific rationale for accepting lower standards for institutions in other countries, this knowledge should reinforce the fundamental thrust of the equivalent protections regulation, which is that different procedures, if thoughtfully and sensibly developed and applied, might offer at least equivalent prospect that the intended protections will be achieved.

Several specific examples will help to illustrate the way the framework is intended to be applied. As we have discussed above, the equivalent protections regulation itself (45 CFR § 46.101(h)) cites the Declaration of Helsinki as a document that might be adopted by a foreign institution seeking equivalent protections status. Yet the Declaration of Helsinki is constructed to function as guidance to investigators and does not explicitly address the responsibilities and accountability of the research institution [9]. Therefore, although the Declaration of Helsinki provides content that is relevant for the substantive judgments that IRBs are required to make about minimizing risk, ensuring that risks and potential benefits are appropriately balanced, and ensuring fair subject selection, it does not explicitly require institutions to foster expectations of ethical conduct and due diligence, nor ensure the appropriate authority for their IRB or Research Ethics Committee.

Likewise, the International Council on Harmonization Harmonized Tripartite Guideline: Guideline for Good Clinical Practice (ICH-GCP) [10] was cited by Dickens [5] as another document that might satisfy the procedural requirements of equivalent protections. Although it covers most of the same (or largely similar) procedural requirements as 45 CFR 46, it does not include procedures that address the institutional responsibilities laid out in 45 CFR 46. Similarly the WHO/TDR Operational Guidelines for Ethics Committees that Review Biomedical Research [11] cover many of the same procedures for research ethics review covered in 45 CFR 46, but do not include explicit guidance related to institutional responsibilities like those in 45 CFR 46.

Although these documents do not appear to explicitly address the full range of protections described in 45 CFR 46, we do not believe that this undermines their critical role as international guidance documents. With the clear recognition of the institutional protections that 45 CFR 46 requires, it should be possible for institutions to adopt specific procedures to satisfy these protections even if they are not addressed specifically in any given guidance document.

4. Approval by the relevant department or agency head for the substitution of the institutional procedures in lieu of those of 45 CFR 46

Based on a recommendation from OHRP following the comparison of the protections provided by the institution's procedures and 45 CFR 46, the Secretary of the Department of Health and Human Services (DHHS) may find that the institution's procedures provide at least equivalent protections and approve the substitution of these procedures in lieu of those of 45 CFR 46. There is some disagreement about the impact of this approval. The NBAC report states that a formal determination of equivalent protections for a given institution would "obviate the need for assurances, and, as a result, OHRP would have to relinquish its oversight authority." [NBAC, Ch. 5, p. 87] This reading relies on the fact that the requirement that the institution enter into an assurance agreement with OHRP is itself a provision of 45 CFR 46, i.e., the very policy that would be substituted for.

In our view, NBAC incorrectly conflated the waiver of regulatory requirements for a particular research project and the assurance given by an institution that the regulations will be followed as part of its normal practice. The substitution provided for in 45 CFR 46 § 101(h) is for the relevant procedures, not for the entire regulatory scheme. The obligations on OHRP to obtain such an assurance, and to enforce compliance with the terms of the assurance, are statutory requirements of the Public Health Service Act [12]. Neither the Department of Health and Human Services' authority to promulgate regulations, nor its authority under 45 CFR 46 §101(h) (the equivalent protections regulation) include authority to eliminate a statutory requirement. The NBAC conclusion also rests on the argument that under the Federal policy a finding of equivalent protections would take the institution beyond the reach of the policy. We believe that a decision about equivalent protections made within the federal policy cannot place an institution outside the scope of the policy.

In addition, we do not believe that the determination of equivalent protections itself implies any surrender, by OHRP, of oversight authority, as implied by the NBAC statement. We recommend, instead, that the "substitution of the foreign institution's procedures" be understood to entail the substitution of one set of procedures designed to assure the appropriate regulatory authorities of the institution's ability and willingness to comply with the Common Rule requirements, with a broader determination that the specific procedures adopted by the foreign institutions—if they differ from those of 45 CFR 46—are at least as likely to bring about the protection of the rights and welfare of research subjects. We do not believe that substitution should be read to imply that OHRP

must relinquish its general regulatory oversight authority for publicly funded research. In fact, we believe that the authority of OHRP to conduct on-going assessment of the equivalence of the institution's procedures and protections is itself a protection implied in 45 CFR 46 (see Table 1).

5. Assurance

A limitation of any system of protection of human subjects is the potential for a gap between policies, as articulated and promoted within institutions, and practice, i.e., the behavior of the investigators, research ethics review committee members, and senior administrators who are charged with the responsibility of implementing the policies. Since this problem is not unique to foreign institutions, the equivalent protections process should not impose more stringent standards than exist in 45 CFR 46. Although it may seem reasonable, on its surface, to expect that policies and procedures for the protection of human subjects may be less familiar in developing country institutions than they are in the United States, and therefore less likely to direct the appropriate action, the comparison of deficiencies in foreign and domestic investigator inspections by the Food and Drug Administration (FDA) in the OIG Report [2, p. 25, Table 2] suggests the need to resist this type of blanket assumption.

An assurance is a legal promise to comply with certain conditions attached to the provision of U.S. federal research funding. This mechanism is the cornerstone of the domestic system in the U.S., formalizing the relationship of accountability between the institutes that receive federal funding and the Office for Human Research Protections, whose mandate involves ensuring that the recipient institutions comply with the regulations. In this respect, the use of an assurance mechanism to formalize equivalent protections is non-discriminatory; it would simply hold foreign research institutions to the same standards of accountability, through the same mechanism, as domestic institutions. As well, the OIG report specifically identified this type of promissory mechanism as one that is underrepresented in the context of international research, but that might offer some improvements in human subject protections, presumably by formalizing relationships of accountability.

Since freedom from the assurance with OHRP was suggested by NBAC as a potential benefit of decisions about equivalent protections for foreign institutions, our position raises the question of what advantage these institutions might gain if the assurance remains a requirement, as our approach would advocate? Determinations of equivalent protections would offer an important symbolic gesture on the part of the United States to foreign countries, namely the recognition that the same ethical goals can be met through procedures different from those in 45 CFR 46. This is a non-trivial gesture, though it would be easy to underestimate its importance for developing countries, in particular. Although many believe that the emphasis on individual autonomy reflected in the U.S. regulations, in particular the provisions on individual informed consent, is likely to be unfamiliar and therefore inconsistent with common decision making practices in many developing countries, there is no evidence of a wholesale rejection by foreign countries of

the ethical ideals and aspirations embodied in the U.S. regulations. On the contrary, there is an extremely active global community working to improve systems of human research protections and the ethical conduct of research. Permitting foreign country institutions to use their own procedures (if found equivalent) would amount to recognition, not just of the procedures themselves, but also of the moral authority of the institutions and/or the national agencies that promulgate the local procedures and guidelines.

Since assurances will still be required, even after a determination of equivalent protections is made for a given institution, the recent move by OHRP to consolidate and streamline its assurance process may turn out to have been timely and sound strategically. The Federal Wide Assurance (FWA), which is currently the main instrument by which assurances are made with OHRP [13], already performs the assurance function with foreign institutions, though a formal comparison of protections in the way we have described above has not been conducted under the current scheme. The familiarity of the FWA and a move to formal recognition of other institutions' (and in many cases countries') guidance and procedures might result in an important opportunity for OHRP to enhance its international education activities by increasing its emphasis on the importance of institutional leadership and accountability in the protection of human research subjects, a message that is equally important to the OHRP mandate domestically.

Along these lines, the World Health Organization is currently working with several countries to examine approaches to protecting human subjects within health research systems. It is likely that OHRP could participate in, or follow closely, some of the pilot studies that will be conducted in developing countries that aim to gain better understanding of human subject protections in these countries. Furthermore, OHRP may wish to consider a strategic initiative aimed at supporting research and evaluation of foreign research institutions. Such an initiative might offer a critical impetus for institutions and countries to focus energy and resources on improving their systems, particularly the aspects relating to institutional accountability, that are critical to equivalent protections, but have been under-represented in international guidance to date.

DISCUSSION

There are several issues related to equivalent protections that we have not resolved in this report. Perhaps the most difficult issue relates to situations in which OHRP might have concerns about an institution's ability to achieve the kinds of accountability required by 45 CFR 46. In some developing countries, for example, prevailing socioeconomic and political conditions may undermine transparency or fairness in social transactions and make the kind of formal accountability relationship required by equivalent protections difficult to achieve. The relationship between the background circumstances of economic, social and political development and the ability of institutions to achieve meaningful accountability is not a clear one [14, 15], but the threat that these circumstances might compromise human subject protections is real and must be given due consideration. It is likely that the most viable approach, at least in the short term, will be for OHRP to

exercise some discretion within the *in toto* assessments of the protections related to institutional accountability (as we have described above). In the longer term, we are hopeful that increased attention to accreditation and work currently underway by the WHO to characterize the ethics function of health research systems and means of assessing their effectiveness might provide tools that will assist OHRP in making these judgments, but for now we believe it is simply not possible to provide clear and reliable guidance on this point.

Most research related to global health involves some sort of collaboration between institutions in sponsoring countries and institutions in affected areas, most often in developing countries. Strong collaborative relationships may provide opportunities to address ethical challenges in ways that would not be possible in their absence. For example, collaborating institutions may establish joint practices for the review and approval of collaborative human subjects research protocols. In doing so, the institutions may improve their IRBs' communication with one another and enhance their understanding of the host country circumstances that might influence the local IRB's decision-making. In this way, the institutions may provide a solution to the problem of disagreements between the local and remote IRBs while retaining their individual discretion to review and disapprove protocols within the scope of 45 CFR 46 [16]. Furthermore, such relationships may also serve to address other complex challenges in research ethics that are unlikely ever to be achieved through unilateral action, such as determining fair and appropriate benefits to the participants and host communities, acceptable standards of care in clinical trials, and what will constitute fair access to interventions at the conclusion of trials. Such collaborative relationships might serve another, perhaps less obvious, function. In relationships that are built on strong commitment to guiding principles of conduct, there is also the potential for the collaborative relationships themselves to promote the value of ethical conduct within the institutions and thereby enhance the capacity of both institutions to ensure that research is being conducted according to agreed-upon standards and with sufficient care and diligence.

The emphasis on regulatory compliance in the U.S. system is seen by some as excessive and contributing to the erosion of skillful judgment and appropriate discretion on the part of investigators and IRBs in determining the ethical acceptability of research with human subjects [17]. The focus on the protections that the regulations aim to achieve offers a clear reminder that the regulations *require*, rather than permit, the judicious and skillful application of reasoning in making determinations such as the appropriate balance of risks and benefits and whether the selection of subjects in any trial has been approached fairly. In this way, it is conceivable that the exercise of developing an approach to equivalent protections might also help to reinforce the underlying ethical architecture of the regulatory system and promote a better appreciation that the regulations require judgment within strong relationships of accountability.

Since 45 CFR part 46 contains 4 separate sub-parts the question arises whether equivalent protections requires separate coverage of each sub-part in the institutions' procedures? Sub-parts B, C and D address research with children, pregnant women and their fetuses

and prisoners, populations that are generally considered to be vulnerable to exploitation in research as a result of deficiencies in autonomy or power that follow from their life circumstances. Although there are specific procedural requirements for each of these sub-populations, we believe the overarching principle with respect to the protection the sub-parts offer is that institutions and their IRBs must ensure that the research ethics review and study oversight are commensurate with the risk and vulnerability of the study population.

We are well aware that there are countries in the world, for example Denmark, in which most research ethics review is conducted at a regional level and not primarily in the host institution. This raises the question of whether it is appropriate to grant equivalent protections status to the institution in this case, or whether some other recognition of the regional research ethics review committee would be required.

Our proposed approach makes it clear that the principal responsibility for ensuring adequate protection of human subjects lies with the research institutions that accept funding for the conduct of research, whatever their particular form or organizational structure might be. Specifically, it is the responsibility of the institution to ensure that the research ethics committee is appropriately independent and adequately qualified and represented to ensure high quality review, even in circumstances in which these activities are organized at regional, or even national, levels. Institutions usually exercise these responsibilities within their domestic systems by following the national laws or requirements that give the regional or national committees authority. In this way, the institution's assurance with OHRP would have the additional force of these domestic rules. This situation is analogous to U.S. institutions that hire private, for profit, IRBs to conduct their reviews, but retain the ultimate responsibility for protecting human subjects in research conducted under their auspices. For these reasons, we believe that the institution remains the appropriate locus for equivalent protections, though the necessary information about the relevant procedures employed by regional, national or other committees located outside the institution, would also figure into the equivalent protections assessment.

Finally, the explicit recognition of institutional responsibility and accountability in 45 CFR 46 illustrates a minor point of divergence between the U.S. regulations and the major international (and national) guidelines. OHRP might take a proactive role in promoting the importance of institutional responsibilities in its international educational activities and perhaps also in its on-going dialogue with the organizations responsible for the international guidelines.

SUMMARY

The Common Rule regulations governing research with human subjects, at 45 CFR 46 § 101(h), include a provision that would allow the U.S. government to determine whether the procedures adopted by a research institution in a foreign country provide protections for human subjects that are at least equivalent to those provided by the U.S. regulations.

Although this authority has not been formally utilized by the U.S. government, we believe that equivalent protections is a feasible strategy for ensuring the protection of human subjects in research conducted in, or through, foreign research institutions and financed by U.S. public funds.

The primary focus of the U.S. policy is the accountability of the research institution for the welfare and rights of human subjects. The overarching goal of the specific accountability mechanisms and procedures described in the policy is to establish expectations of ethical conduct within the research institution. The responsibility for achieving these aims is shared by the institution, the Institutional Review Board (IRB) or Research Ethics Committee (REC), and the relevant U.S. Agency or Department head. Although investigators are critical actors in achieving these goals, the policy provides very little explicit guidance to investigators and therefore suggests that the protection of human subjects depends largely on the proper promotion and conscientious execution of standard practices and procedures, including those related to research ethics review, within the institution.

We have proposed an approach to equivalent protections that involves 5 separate steps, the first 4 of which are steps in determining the equivalence of the protections offered by procedures employed in foreign research institutions, and the last of which involves an assurance that these procedures will be followed within the institution:

Steps in determining equivalence

(1) Articulation of the specific protections embodied in 45 CFR 46
(2) Assessment of the protections provided by the institution's procedures
(3) Comparison of the protections provided by the institution's procedures with those provided by 45 CFR 46 and determination of equivalence, or not
(4) Approval of the relevant department or agency head for the substitution of the institutional procedures in lieu of the procedures of 45 CFR 46

Mechanism of assurance

(5) Assurance from the institution that the substituted procedures will be followed in the conduct of human subjects research funded by the U.S. Department of Health and Human Services (DHHS).

In our analysis, we have been able to identify 7 specific protections afforded by 45 CFR 46 that should figure in the determination of equivalence:

- Establish expectations of ethical conduct and due diligence in review and performance of research within the institution.
- Ensure adequate authority and independence of the IRB/Research Ethics Committee
- Protection from biased and arbitrary decisions in research ethics review
- Ensure sufficient quality and comprehensiveness of research ethics review
- Ensure review and oversight are commensurate with risk and vulnerability of study population
- Protection from unnecessary or unjustified risk throughout the course of the study

- Protection from inadequate disclosure and non-voluntary participation

We believe that each of these protections is necessary for a determination of equivalent protections. We also believe that each protection may be achieved in a number of different ways, including the use of procedures that differ from those provided in 45 CFR 46. In making determinations of equivalence, the Office for Human Research Protections (OHRP) should assess whether the procedures employed by the foreign institution are able to satisfy each of these protections individually and in aggregate.

Based on a recommendation from OHRP following a comparison of the protections provided by the institution's procedures and 45 CFR 46, the Secretary of DHHS may find that the institution's procedures provide at least equivalent protections and approve the substitution of these procedures in lieu of those of 45 CFR 46. We do not believe that the determination of equivalent protections itself implies any surrender, by OHRP, of oversight authority for DHHS funded research conducted within the institution. The authority of OHRP to conduct on-going assessment of the equivalence of the institution's procedures and protections is itself a protection implied in 45 CFR 46, though not one that figures in an assessment of the protections provided by an institution's procedures.

The substitution of the foreign institution's procedures in lieu of those of 45 CFR 46 does not obviate the need for the institution to enter into an assurance with OHRP that the procedures will be followed by the institution in the conduct of DHHS funded research. An assurance is a legal promise to comply with certain conditions attached to the provision of U.S. federal research funding. This mechanism is the cornerstone of the domestic system in the U.S., formalizing the relationship of accountability between the institutions and OHRP, whose mandate involves ensuring that the recipient institutions comply with the regulations. In this respect, the use of an assurance mechanism to formalize equivalent protections is non-discriminatory for foreign institutions, since it would hold them to the same standards of accountability, through the same mechanism, as domestic institutions in the U.S.

Determinations of equivalent protections would offer an important symbolic gesture on the part of the United States to foreign countries, namely the recognition that the same ethical goals can be met through procedures different from those in 45 CFR 46. Permitting foreign country institutions to use their own procedures (if found equivalent) would amount to recognition, not just of the procedures themselves, but also of the moral authority of the institutions and/or the national agencies that promulgate the local procedures and guidelines.

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APPENDIX