Putting International Research Ethics Guidelines To Work for the Benefit of Developing Countries

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It has become increasingly well-recognized in recent years that an equitable distribution of the benefits of research is an important component of international research ethics.[1] International research ethics guidelines, in particular the World Medical Association's *Declaration of Helsinki*,[2] the Council for International Organizations of Medical Sciences's (CIOMS) *International Ethical Guidelines for Biomedical Research Involving Human Subjects*,[3] and the United Nations Joint Programme on AIDS's (UNAIDS) *Ethical Considerations in HIV Preventive Vaccine Research*,[4] have begun to assign investigators and their sponsors the task of ensuring and realizing research-related benefits for host country research subjects and their communities. These agreements impose these obligations through three primary requirements: the negotiation of agreements about the conditions under which the research will occur prior to the start of the research, the assurance of research subjects' post-trial access to effective research interventions, and the establishment of efforts to build the

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1. *Fair Benefits for Research in Developing Countries*, 298 SCIENCE 2133, 2133-34 (2002) [hereinafter *Fair Benefits*]; Leonard H. Glantz et al., *Research in Developing Countries: Taking "Benefit" Seriously*, HASTINGS CENTER REP., Nov. 1998, at 38, 38-42.

2. WORLD MED. ASS'N, DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (2002), http://www.wma.net/e/policy/pdf/17c.pdf (last visited May 1, 2004).

3. COUNCIL FOR INT'L ORGS. OF MED. SCIS. (CIOMS), INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (2002), http://www.cioms.ch/frame_guidelines_nov_2002.htm (last visited May 22, 2004).

4. UNAIDS, ETHICAL CONSIDERATIONS IN HIV PREVENTIVE VACCINE RESEARCH 15-16 (2000), http://www.unaids.org/EN/other/functionalities/advancedSearch.asp (last visited Apr. 18, 2004).

capacity of researchers and their institutions in host countries to participate as full partners in the research.[5] Although the ethical need for such obligations is indisputable, these obligations present the possibility of expanding the role of investigators in a way that might be unrealistic and therefore of limited effectiveness in ensuring the fair distribution of research benefits. Despite these reasonable concerns about feasibility, investigators may be particularly well placed to play an enhanced role in maximizing the benefits of research in low- and middle-income countries (LMIC) as a result of their unique position in the global health workforce.

In this Commentary I argue that, under appropriate circumstances and with the appropriate training and support, investigators may be able to play a critical role in ensuring that communities in LMIC that participate in international collaborative research derive a fair share of the benefits of the research and thereby avoid being exploited. More specifically, I argue that the main activities that are required by collaborative partnership in research—engagement and negotiation—also serve as the basic means by which a fair distribution of research benefits may be achieved. If investigators can be assured appropriate training and supportive mechanisms, and if some necessary changes in research ethics review can occur, investigators may collectively represent a potent global force for ensuring access to research benefits.

I. THE NEED TO AVOID EXPLOITATION

The past decade has seen an unprecedented expansion in international health research, particularly clinical drug and vaccine trials funded by sponsors in high-income countries (HIC) and conducted in low- and middle-income countries (LMIC).[6] At any given time in locations

5. For a detailed discussion of prior agreements, see Alice K. Page, *Prior Agreements in International Clinical Trials: Ensuring the Benefits of Research to Developing Countries*, 3 YALE J. HEALTH POL'Y L. & ETHICS 35 (2002). For a recent discussion of post-trial obligations in international guidelines, see WORLD MED. ASS'N, WMA SECRETARIAT REPORT ON THE REVISION OF PARAGRAPH 30 OF THE DECLARATION OF HELSINKI (2003), http://www.wma.net/e/ethicsunit/pdf/secretariat_report_rev_paragraph30.pdf (last visited Apr. 2, 2004); and WORLD MED. ASS'N, DOCUMENTATION FOR THE PREPARATION OF NOTE OF CLARIFICATION ON PARAGRAPH 30 OF THE REVISED DECLARATION OF HELSINKI, http://www.wma.net/e/ethicsunit/pdf/preparation_clarification_paragraph30.pdf (last visited Apr. 2, 2004). For capacity-building requirements, see CIOMS, *supra* note 3, at Guideline 20; and UNAIDS, *supra* note 4, at 15-16.

6. Solomon R. Benatar, *Avoiding Exploitation in Clinical Research*, 9 CAMBRIDGE Q. HEALTHCARE ETHICS 562, 562-65 (2000).

around the world, there are thousands of researchers from institutions, agencies, and private companies in HIC conducting research in LMIC.[7] The proportion of international health research that is funded by private industry sponsors has also increased. In 1992, private pharmaceutical companies accounted for about forty-four percent of global spending on health research,[8] and a decade later the proportion has been estimated at nearly half of the seventy billion dollars spent globally on health research.[9] Greater awareness of this expansion of private interests, in particular, has helped to focus attention on global health disparities and the vastly disproportionate levels of funding devoted to research on the diseases that burden HIC compared to those of LMIC.[10]

The recognition of the nature and extent of disparities in health and health research funding has also framed a long-standing debate over the ethics of international research. At the core of this debate is the question of what investigators and sponsors from HIC owe to the subjects of clinical research conducted in LMIC, where the entitlements to, and availability of, healthcare are often inferior to those in the sponsoring HIC.[11] The debate has resulted in heightened awareness of the potential for international health research to be exploitative of host country communities and populations.[12] Although exploitation is a difficult concept to define

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7. The World Bank classifies economies into low-income, middle-income, and high-income groups based upon per capita gross national income (GNI). Low-income and middle-income economies, which are also sometimes referred to as developing economies, are those whose per capita GNI is less than $9206. All of the African nations fall under this category, as well as the majority of countries in Central and South America, Central and Southern Asia, and Eastern Europe. High-income countries (those with per capita GNI greater than $9206) include those in North America and Western Europe, as well as some Asian and Middle Eastern nations, such as Australia, Bahrain, China, Israel, Japan, Taiwan, and the United Arab Emirates. For more detailed information, see WORLD BANK, CLASSIFICATION OF ECONOMIES, http://www.worldbank.org/prospects/gep2003/classification.pdf (last visited Apr. 2, 2004).

8. *See* Benatar, *supra* note 6, at 563.

9. MSF ACCESS TO ESSENTIAL MEDICINES CAMPAIGN, DRUGS FOR NEGLECTED DISEASES WORKING GROUP, A SURVEY OF PRIVATE SECTOR DRUG RESEARCH AND DEVELOPMENT: FATAL IMBALANCE: THE CRISIS IN RESEARCH AND DEVELOPMENT FOR DRUGS FOR NEGLECTED DISEASES 16-20 (2001) [hereinafter SURVEY], http://www.accessmed-msf.org/documents/fatal_imbalance_2001.pdf (last visited Apr. 18, 2004).

10. GLOBAL FORUM FOR HEALTH RES., THE 10/90 REPORT ON HEALTH RESEARCH xi (2000).

11. Solomon R. Benatar & Peter A. Singer, *A New Look at International Research Ethics*, 321 BRIT. MED. J. 824, 824-26 (2000).

12. *See* Benatar, *supra* note 6.

precisely,[13] it has been described as an unfair distribution of the benefits of research in the context of international collaborative research.[14] The definition continues to garner attention[15] and is likely to be refined further over time.

Whatever the appropriate definition of exploitation, the history of international health research is blemished by poor performance in the transfer of benefits to the communities in LMIC that have served as the proving grounds of interventions of interest, particularly novel drugs and vaccines.[16] Most privately-funded research involves the testing of drugs and interventions that will be sold exclusively in HIC and, as such, will serve only to widen disparities in global health and health research funding. Currently, Africa, which is home to roughly fourteen percent of the world's population and its greatest burden of disease, including just under thirty million people living with HIV/AIDS,[17] accounts for less than two percent of the world market for drugs.[18] North America, Europe, and Japan, collectively with less than 1.5-times the population of Africa, account for more than forty times more, or eighty percent, of the global market.[19]

II. BACKGROUND

A. The Current Emphasis in International Research Ethics

In response to the debate about exploitation in international heath research, and the research involving drug and vaccine trials in particular, there has been a rapid and concerted expansion of major international research ethics guidelines[20] and a proliferation of commissioned analyses

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13. *See generally* ALAN WERTHEIMER, EXPLOITATION 10-12 (1999) (examining the complexity of the concept of exploitation).

14. *See Fair Benefits, supra* note 1, at 2133.

15. *See* JENNIFER HAWKINS & EZEKIEL J. EMANUEL, EXPLOITATION IN MULTINATIONAL CLINICAL RESEARCH (forthcoming 2005).

16. Reidar K. Lie, *Justice and International Research, in* BIOMEDICAL RESEARCH ETHICS: UPDATING INTERNATIONAL GUIDELINES. A CONSULTATION 27 (Robert J. Levine & Samuel Gorowitz eds., 2000).

17. *Global Estimates for Adults and Children, End 2003*, UNAIDS, http://www.unaids.org/wad/2003/Epiupdate2003_en/Epi03_11_en.htm#P251_74233 (last visited Apr. 2, 2004).

18. Amy Kapczynski et al., *Global Health and University Patents*, 301 SCIENCE 1629, 1629 (2003).

19. *See* SURVEY, *supra* note 9, at 16.

20. *See supra* notes 2-4 and accompanying text.

of the related ethical issues.[21] High-profile national and international bodies have conducted many of these analyses. The latest flurry of guidelines and analyses has focused squarely on the unfair distribution of benefits of research and emphasized the critical role of procedural safeguards against the exploitation of host country populations. Yet, the implications of this current emphasis are poorly understood. Guidelines on three main issues—negotiation of prior agreements, capacity-building, and post-trial obligations—are of interest here, since they may be most likely to involve considerable expansion of investigators' current roles.

Current international guidelines (e.g., the *Declaration of Helsinki*, the CIOMS *Guidelines*, and the UNAIDS *Ethical Considerations*) include provisions that require researchers from HMIC to negotiate with the host country collaborators about the conditions under which the research will be conducted, including what benefits are expected to accrue to the host communities, prior to the start of the research. They also include provisions about the assurance of on-going access to any intervention demonstrated to be effective through the course of the study. These assurances are commonly known as "post-trial obligations." The guidelines also state that, in the course of research activities, opportunities must be found to enhance the capacity of the LMIC collaborators and their institutions to conduct and be full partners in research.[22]

Since the main guidelines lack specificity about how the responsibility for these provisions should be divided between investigators and research sponsors, it is not yet clear whether, or to what extent, current mechanisms of review will enable Institutional Review Boards (IRBs) or Research Ethics Committees (RECs) in HIC to assess the extent to which current investigators are executing these provisions, or whether they will instead have to begin to require new formal demonstration that the requirements have been met. While this question has received little attention to date, the answer is of considerable consequence: On the one hand, these obligations could prove to be burdensome, and even deleterious to the research effort; on the other hand, if investigators were able to meaningfully fulfill these obligations, the benefits to LMIC could be significant. Whether the

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21. *See* U.S. NAT'L BIOETHICS ADVISORY COMM'N, ETHICAL AND POLICY ISSUES IN INTERNATIONAL RESEARCH (2001), http://www.georgetown.edu/research/nrcbl/nbac/human/overvol1.pdf; U.K. NUFFIELD COUNCIL ON BIOETHICS, THE ETHICS OF RESEARCH RELATED TO HEALTHCARE IN DEVELOPING COUNTRIES (2002), http://www.nuffieldbioethics.org/filelibrary/pdf/errhdc_fullreport.pdf.

22. *See, e.g.*, CIOMS, *supra* note 3, at Guideline 20.

benefits to LMIC exceed the costs to investigators—and how the costs to investigators could be minimized while ensuring the effectiveness of these obligations—are questions I take up later in this Commentary.

B. Guidelines and Legal Requirements

Rules and conventions governing research with human subjects are managed differently in different countries. In the United States, these rules are codified into federal regulations that must be followed by institutions and investigators to ensure their eligibility to receive public funding for their research activities.[23] In contrast, international guidelines such as the *Declaration of Helsinki*, the CIOMS *Guidelines*, and the UNAIDS *Ethical Considerations* are not legally binding documents.[24] Instead, they represent different (and occasionally conflicting) perspectives about what principles and actions are necessary for research to be considered ethical. Each reflects the perspective of its constituent groups (e.g., national medical associations, in the case of the *Declaration of Helsinki*), and the force of the guidelines depends in large measure on current global opinion about the moral authority of the promulgating agencies. In this respect, the guidelines cannot be considered to be requirements in the same sense that the U.S. federal regulations can. However, ethics is largely about the establishment and justification of conventions of practice, and in this sense it is worth remembering that some of the specific provisions of the U.S. regulations,[25] such as the requirement of review by an independent committee, were required in a moral sense by the *Declaration of Helsinki* prior to their formal adoption into U.S. law.

The converse may be true to some extent as well. For example, Jonathan Moreno has argued that the increasingly intense regulation of research involving human subjects in the United States risks eliminating whatever is left of investigators' discretion to make ethical judgments about the protection of human subjects,[26] and could reduce research ethics to a rote exercise of ensuring compliance with the letter of the law. For many, this trend has progressively undermined the moral authority of the regulations. What is left, particularly in the context of international

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23. *See* 46 C.F.R. § 46.101 (2003).

24. David P. Fidler, *"Geographical Morality" Revisited: International Relations, International Law, and the Controversy over Placebo-Controlled HIV Clinical Trials in Developing Countries*, 42 HARV. INT'L L.J. 299, 324-28 (2001).

25. 45 C.F.R. § 46.109(a) (2003).

26. Jonathan D. Moreno, *Goodbye to All That: The End of Moderate Protectionism in Human Subjects Research*, HASTINGS CENTER REP., May-June 2001, at 9, 9-17 (2001).

collaborative research, is an awkward marriage between non-binding international guidelines with some reasonably legitimate claims to moral authority in the protection of human subjects[27] and legally required regulations that some view as having diminishing moral authority.

Arguably, however, the tension between these types of documents may not be as great as it initially appears to be. Despite the prevailing culture of regulatory compliance described by Moreno, the regulations themselves require judgment, particularly with respect to the balance of risks and benefits, and the international guidelines provide principles and analyses that may help the IRBs to make these judgments in their reviews of international research, particularly collaborative research in LMIC. To the extent that the international guidelines diverge on important substantive issues, their value for IRBs may be reduced. But for prior agreements, capacity-building, and post-trial obligations, there is at least some agreement in principle among the guidelines, even if the specific responsibilities and details of implementation remain somewhat underdeveloped. Although there may be other strategies that could help improve the effectiveness of U.S. IRBs in their review of international research,[28] these strategies may add little substantive content to the existing guidance on prior agreements, post-trial obligations, and capacity-building.

III. ENGAGEMENT, NEGOTIATION, AND AN EXPANDED ROLE FOR INVESTIGATORS

Although the guidelines vary in the extent to which they describe specific responsibilities for various parties, the obligations associated with prior agreements, post-trial obligations, and capacity-building are generally directed toward research sponsors and other groups who may have the means and authority to commit resources to satisfy these requirements.[29]

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27. It is important to recognize that some see this authority as having been compromised to some extent by contentious recent revisions. *See* Heidi P. Forster et al., *The 2000 Revision of the Declaration of Helskini: A Step Forward or More Confusion?* 358 THE LANCET 1449, 1449-52 (2001).

28. *See, e.g.*, Eric M. Meslin et al., International Research Ethics: Building Capacity from the Ground Up (2004) (unpublished manuscript, on file with *Yale Journal of Health Policy, Law, & Ethics*) (discussing efforts to "develop[] a collaborative approach . . . for conducting research that is sensitive to local values and consistent with accepted principles of research ethics" between a U.S. university and a partner research institution in Africa).

29. For example, the CIOMS Guidelines state that "Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that . . . any intervention or product developed, or knowledge

There is a logic to a broad base of accountability, but it tends to obscure the way that these obligations are satisfied in practice. Research sponsors may be actively engaged in some of these activities, particularly in large-scale and high-budget research projects, but for smaller research projects, they are typically carried out on a day-to-day basis by the investigators themselves with only limited involvement from the agencies sponsoring the research. And so, although the guidelines may not explicitly ascribe the ethical responsibilities for these requirements to investigators, those responsibilities generally fall to investigators because of the way the allocation of responsibilities in research works in practice.

Generally speaking, the specific activities in question may be thought to fall under the rubric of collaborative partnership, a set of activities whose ethical relevance to international research is increasingly recognized,[30] but whose practices are only beginning to be described in

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generated, will be made reasonably available for the benefit of that population or community." CIOMS, *supra* note 3, at Guideline 10. Also on the topic of ensuring availability, the UNAIDS Vaccine Guidelines state that

> [t]his discussion should include representatives from relevant stakeholders in the host country, such as representatives from the executive branch, health ministry, local health authorities, and relevant scientific and ethical groups. It should also include representatives from the communities from which participants are drawn, people living with HIV/AIDS, and NGOs representing affected communities.
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> Furthermore, the discussion concerning availability and distribution of an effective HIV vaccine should engage international organizations, donor governments and bilateral agencies, representatives from wider affected communities, international and regional NGOs and the private sector. These should not only consider financial assistance regarding making vaccines available, but should also help to build the capacity of host governments and communities to negotiate for and implement distribution plans.

UNAIDS, *supra* note 4, at 14. Although the Declaration of Helsinki focuses explicitly on the obligations of the physician investigator, paragraph 30, which deals with ensuring on-going access, does not ascribe responsibility to any specific party. However, the main thrust of the paragraph suggests a role for the research sponsors and other parties such as those listed in the UNAIDS Guidelines: "At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study." WORLD MED. ASS'N, *supra* note 2, at 4.

30. *See, e.g.*, Bernard Lo & Ronald Bayer, *Establishing Ethical Trials for Treatment and Prevention of AIDS in Developing Countries*, 327 BRIT. MED. J. 337, 337-38 (2003); *see also* J. V. Lavery et al., *Ethical Issues in International Environmental Health Research*, 206 INT'L J. HYGIENE & ENVTL. HEALTH 453, 457-58 (2003) (discussing the significance of community-based approaches in international environmental health research).

detail sufficient to guide the activities of investigators.[31] There are many specific aims of collaborative, or community, partnership, but there are only a few general mechanisms through which it achieves ethical ends, such as ensuring the fair distribution of benefits. Collaboration requires *engagement* with host-country researchers, institutions and governments in LMIC; it requires the sharing, through dialogue, of the relevant concerns, aspirations, motivations, and opportunities that will establish the common goals necessary for research to proceed. But engagement itself does not settle issues about how the various interests of stakeholders in the research (e.g., the investigators, research subjects, community, institutions, and governments) can and should be met, and under what conditions the research activities are most likely to satisfy these multiple interests. Thus *negotiation*, the task of forging agreement on the specific ways in which the relevant interests will be satisfied in the course of the research, is also a critical aspect of collaboration.

Investigators and sponsors from HIC often enjoy relatively high levels of access to senior officials in healthcare and politics in LMICs hosting the research. This access provides opportunities for their engagement and negotiation activities to make a difference for the health of the populations that participate in their research. However, precisely how these opportunities should be sought and managed, especially by less experienced HIC investigators, who lack the extensive contacts and whose relevant skills may be underdeveloped, is not currently a prominent subject of ethical guidance. Although some of the few examples of engagement and negotiation that have been captured in the literature to date involve large-scale multi-million dollar trials with complex and often competing interests among sponsors, communities, and governments, it would be misleading to adopt these trials as paradigm cases.[32] More representative, and collectively also of greater potential impact, are the many thousands of HIC investigators in smaller research initiatives throughout the world, who lack regular recourse to logistical support teams, lawyers, and high ranking host-country officials. If the guidelines are intended to apply equally—or at least proportionately—to their research activities, their circumstances will require specific consideration.

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31. Ezekiel J. Emanuel et al., *What Makes Clinical Research in Developing Countries Ethical?: The Benchmarks of Ethical Research*, 189 J. INFECTIOUS DISEASES 930, 931-32 & tbl. 1 (2004).

32. In her discussion of prior agreements, Page discusses large scale prior agreements using examples from the World Health Organization, the International AIDS Vaccine Initiative, and the California-based company VaxGen, whose candidate AIDS vaccine "AIDSVAX" was first to Phase III efficacy testing. Page, *supra* note 5, at 54-64.

In some respects, it seems unremarkable that investigators are assumed to be the most appropriate protagonists for these collaborative dramas. They are the most knowledgeable about the aims, feasibility, and relevance of the research, and therefore best placed to tell the stories that engagement requires. Additionally, investigators from HIC often begin this process with established relationships with some host country collaborators that they have met through training or professional activities, and therefore may have an "in" with the relevant communities and authorities in the host country, even before initiating a broader engagement. The idea that the investigators from HIC should assume leadership roles with respect to satisfying the current research ethics guidelines related to exploitation and fair distribution of benefits is a reasonable one. But the idea that researchers should shoulder the lion's share of responsibility for effecting these improvements through their work is a potentially insidious one and deserves to be promulgated carefully and deliberately.

IV. "ROLE EXPANSION" AND ITS IMPLICATIONS

If investigators are intended to be the principal purveyors of fair distribution of research benefits in accordance with the current guidelines, and if the ethical motivation behind the guidelines is the same for small-scale research projects as for large ones, then it seems that some expansion of investigators' current roles is inevitable. "Role expansion" in this sense may be a reasonable and feasible extension of the core functions and opportunities of investigators. Moreover, if it is exercised with sufficient care and integrity, it might represent an as yet poorly recognized dimension of human resources mobilization in global health. However, to be utilized to full effect these roles must be made explicit and supported in meaningful ways by research sponsors and institutions. Thoughtful researchers should greet the potential for "mission creep" with some trepidation. Three concerns, in particular, deserve some separate consideration: the potential for dilution of investigators' impact, the fit between the activities required by role expansion and investigators' training, and the unwitting relief of others' obligations.

A. Dilution of Investigator Impact

The main issue related to dilution of investigators' impact is whether, on balance, investigators trying to follow the current requirements in international research ethics can do so without jeopardizing the conduct of their research or the quality of the evidence it generates. In effect, this is a concern about the scarcest of resources: time. The main activities

associated with the current requirements (i.e., engagement and negotiation) will entail even more tasks in schedules that, for many investigators, are already far beyond comfortable management. Investigators, particularly those in the public sector, have heavy demands in reading, academic writing, research grant preparation, reviewing, teaching and mentoring, and committee work, in addition to the myriad demands of designing, conducting, interpreting, and presenting the research itself. For researchers in global health, these demands are often split between institutions on different continents. Concern about adding additional responsibilities to these already busy schedules is clearly warranted.

But it is necessary to look beyond the immediate concern about additional demands on time. It is certainly true, for example, that most investigators conducting collaborative research in LMICs are concerned about—indeed deeply motivated by—the potential impact of their research in the service of improving global health. Rather than diluting their impact by robbing them of invaluable research time, the new requirements might force investigators to consider and even embrace different practices, some of which might actually enhance the impact of their work. It is plausible that requiring investigators to think through the potential benefits of their research in greater detail (i.e., what these benefits are, or could be, and how they might be realized) could enhance the influence of their research, rather than dilute it. In other words, the requirements themselves might force investigators to critically examine—and perhaps find wanting—their current approaches to ensuring that their efforts result in benefits for research subjects and their communities. Of course, there are many investigators who already take these issues very seriously and do an exemplary job. But the historical lack of benefits to LMIC from international health research is evidence enough that existing practices are insufficient.

B. The Fit Between Researcher Training and the New Requirements

Precisely what are researchers being asked to do under the current requirements? Above, I have provided a simplified account that focuses on the two main types of activity associated with prior agreements, capacity-building, and post-trial obligations: engagement and negotiation. On the surface, these may appear to be quite ordinary and common tasks, and it may be tempting for researchers and perhaps also drafters of international research ethics guidelines to underplay their importance and complexity. But in fact, each of these activities might also be the topic of a separate course in an international MBA program or in training for foreign

diplomatic service. Each requires some theoretical foundation, enormous skill, and significant experience if it is to be performed effectively and reliably; together, they could easily consume a huge proportion of a researcher's time—at least through certain critical periods of the research. But although these activities may be well represented in the curricula of schools of law, business administration, and international relations, they are not part of the current landscape in research training programs, even in schools of tropical medicine and hygiene, where the value of these activities might be expected to be better appreciated.[33] The result is that investigators are insufficiently prepared to perform the very tasks that may be necessary to meet the great expectations of current international research ethics guidelines.

Despite these challenges, it is critical to recognize that many researchers are currently performing these, or very similar, roles in the research they conduct in LMIC throughout the world, though the extent of these activities is not known and likely varies with the nature and scale of the research. Although their current effectiveness with respect to these roles is not clear, the community of HIC investigators currently working in LMIC clearly represents an inchoate resource whose potential impact on global health could be great.

C. The Responsibilities of Others

It is a common fear in capacity-building efforts in LMIC—especially those with poor governance and leadership—that foreign workers, including health researchers, engaged in efforts to make the country better may simply be taking on work that the governments, private sector, and civil society of the host country should be doing and from which they should be benefiting.[34] It is less frequently realized that researchers might be able to utilize their standing to encourage otherwise reluctant or

33. In fact, schools of public health and tropical medicine are well placed to incorporate some of these issues into existing programs. A cursory internet search of a few of the world's best known schools identifies courses on topics such as consultation techniques, communication strategy, team management and leadership, and negotiation, though not with an explicit focus on ethics and research benefit sharing.

34. James Pfeiffer, *International NGOs and Primary Health Care in Mozambique: The Need for a New Model of Collaboration*, 56 SOC. SCI. & MED. 725, 725-38 (2003). Pfeiffer focuses on development aid activities conducted by NGOs, but focuses on a number of NGOs, such as USAID, Family Health International and Pathfinder, which regularly sponsor and/or conduct research. He discusses baseline studies, surveys and evaluations as typical activities. *Id.* at 733.

uninterested authorities to get involved in the funding, conduct, or application of research for the benefit of their communities. The fact that this rarely occurs—at least in the straightforward way implied—does not make the point irrelevant. In fact, the history of a dismal failure to realize fair benefits for host countries through research is itself likely to be a potent deterrent for many potential collaborators from LMIC. But as examples of benefits to host country populations from international research emerge, those benefits—even modest ones—will reinforce the value of the current ethical guidelines; when that happens, some of the well-deserved skepticism may begin to recede and open up new space for creative and constructive dialogue. In fact, this possible change may reflect the true potential of the current ethical guidelines, and if so, investigators surely have much to contribute in this respect.

V. CAN THE NEW GUIDELINES ACHIEVE THEIR INTENDED EFFECT?

A. The Magnitude of the Problem

It is important at the outset to recognize the magnitude of the problem that prior agreements, capacity-building, and post-trial obligations aim to address. Although these mechanisms are meant to be applied to health research of all kinds, the global struggle to control HIV/AIDS offers an instructive example of the overwhelming magnitude of the challenge to realize research-related benefits for participating communities. UNAIDS currently estimates that it would cost between seven to ten billion dollars per year to achieve effective control of HIV/AIDS in low- and middle-income countries.[35] The WHO Commission on Macroeconomics and Health estimated that the research and development costs alone for scaling up national health care systems to avert eight million deaths per year globally—many from HIV/AIDS—would be three billion dollars per year by 2007, or approximately eleven percent of its projected total grant assistance of twenty-seven billion dollars for that year. The CMH also proposed 1.5 billion dollars in support for the Global Fund for Health Research and an additional 1.5 billion dollars annually for research and development activities through existing institutions.[36]

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35. United Nations, Calculating the Cost of an Effective Global Campaign Against HIV/AIDS, *at* http://www.un.org/ga/aids/ungassfactsheets/html/fscost_en.htm (last visited Apr. 3, 2004).

36. COMM'N ON MACROECONOMICS & HEALTH, WORLD HEALTH ORG., MACROECONOMICS AND HEALTH: INVESTING IN HEALTH FOR ECONOMIC DEVELOPMENT 13-14 (2001), http://www.un.org/esa/coordination/ecosoc/docs/RT.K.MacroeconomicsHealth.pdf.

Effective control of HIV/AIDS globally will require research on treatment, prevention strategies, health services and policy, palliative care and epidemiology, to name a few specific dimensions. But the scale and diversity of the necessary research agenda also reinforces the idea of the vast collective potential for individual investigators to effect improvements in the transfer of research benefits.

B. Evaluation of Impact

It is conceivable that the current emphasis in international research ethics guidelines could have important implications for the way benefits accrue to LMIC from research collaboration. Any evidence of the effectiveness of these guidelines in reducing exploitation by improving the transfer of research benefits would clearly enhance the perceived value of research ethics in global health, a perception that has suffered from the protracted and occasionally arcane debate over standards of care.[37] Accordingly, the evaluation of these new requirements is a challenge that must be taken seriously. A more concerted effort by global research funders, perhaps in conjunction with the World Medical Association, CIOMS, and UNAIDS, could help to clearly establish the feasibility and value of these new requirements, including their impact on the exploitation of LMIC populations. Along these lines, an international database of prior agreements as well as long-term follow-up on the outcomes of research, including the distribution of benefits, would not only help host countries to document and evaluate the benefits of collaboration, but would also help HIC public sponsors of international research to justify their activities to the governments that allocate their funding. Additionally, this type of information would serve as a valuable resource for U.S. and other HIC IRBs/RECs, which often lack experience reviewing international health research.

VI. CHANGES IN RESEARCH ETHICS REVIEW

The guidelines, on their own, are insufficient to alter well-established practices by both investigators and the committees that review the ethical acceptability of their research. In the case of international guidelines like the *Declaration of Helsinki* and the CIOMS *Guidelines*, the lack of meaningful enforcement mechanisms makes this challenge even greater. Therefore,

37. On some of the reasons behind the difficulty in resolving the disagreements in the standard of care debate, see Alex J. London, *The Ambiguity and the Exigency: Clarifying 'Standard of Care' Arguments in International Research*, 25 J. MED. & PHIL. 379, 379-97 (2000).

other changes in research ethics review are necessary to create meaningful change in this area.

A. The Need for Cultural Change

The current emphasis in the guidelines must be reinforced by cultural changes in research ethics review, particularly in the sponsoring country institutions. IRBs and the relevant regulatory authorities in the United States, in particular, must find ways to move beyond the current preoccupation with informed consent and protectionist postures[38] to grapple more realistically with issues of beneficial impact and social value in research. It is here that ethically significant improvements are most likely to be realized, rather than in marginal improvements to informed consent.

In part, these issues are given short-shrift in research ethics review precisely because they involve complex and difficult judgments about the balance between protecting human subjects, on the one hand, and taking bolder steps to improve the value of research for host country populations, on the other. IRBs need to begin to invest more time and energy into examining, and asking investigators difficult questions about, the potential social value of the research they review, and in particular the nature and extent of the benefits that they reasonably expect to accrue from their research activities. Emerging frameworks and concrete benchmarks for collaborative partnership might be particularly valuable in this respect.[39]

Where researchers are not forthcoming about how they see their research activities leading to benefits for the populations under study, IRBs should be proportionately circumspect about the value of the research. Importantly, this should not prejudice IRBs against preliminary studies, Phase I trials, or other studies for which the immediate benefits may be more difficult to anticipate. Rather, it should mark a change in the culture and attitude of IRBs away from unduly intense scrutiny of techniques, such as informed consent, that may, in fact, offer limited protection from exploitation[40] to greater emphasis on areas such as the planning and distribution of benefits of research that might prove to be more effective at reducing exploitation. Regulatory authorities, such as the Office for Human Research Protections (OHRP) in the United States, could play an

38. *See* Moreno, *supra* note 26.

39. *See* Emanuel et al., *supra* note 31, at 930-32.

40. Christine Pace et al., *What We Don't Know About Informed Consent*, SciDevNet, *at* http://www.scidev.net/dossiers/index.cfm?fuseaction=dossierreaditem&dossier=5&type=3&itemid=189&language=1 (last visited Apr. 3, 2004).

important role in facilitating this cultural evolution by emphasizing the importance, and regulatory requirement, of judgments in research ethics review and by supporting programs to encourage increased sophistication and excellence in these judgments by IRBs.[41]

B. Supportive Teams

If it is accepted that researchers are well-placed to participate in the engagement and negotiation activities that the current international guidelines specify, and yet are unlikely to be maximally effective in these endeavors on their own, then the question becomes: How might investigators best be supported in satisfying these requirements? It is conceivable that expert teams could be developed with skills and experiences related to the core functions of engagement and negotiation. These teams might be attached to an international agency whose recognized mandate involves the protection of human subjects in research. They might be available to investigators and sponsors for consultations related to individual studies or research programs and would bring to bear the relevant expertise, experiences and, ideally, knowledge of local culture and politics, in lending assistance for research in LMIC. It is perhaps more likely that the cost of these services could become allowable research expenses if there was agreement among the world's major health research funding bodies on their value. Given the importance of relationships in facilitating engagement and forging trust in negotiations,[42] it is conceivable that sponsors could even enhance the value of their investments in health research by providing some appropriate funding programs aimed explicitly at relationship building and engagement. The fact that these proposals currently sound far-fetched and impractical should not disqualify them outright from further consideration. It may be that it is precisely the lack of this type of supportive mechanism, along with the laissez faire application of international guidelines on research benefits, that has permitted international health research to flourish for so long without meaningful benefits to LMICs.

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41. *See* United 45 C.F.R. § 46.111a(2) (2003). This regulation discusses the responsibility of Institutional Review Boards with respect to risk and benefit in research, which states that IRBs must determine that "[r]isks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result." *Id.*

42. Page, *supra* note 5, at 65 (emphasizing the importance of the strength of the collaborators' relationships and mutual commitment to shared goals, since many agreements proceed slowly on a verbal basis).

C. Training for Investigators

It is a relatively recent phenomenon that researchers are required to complete training in research ethics as a condition of receipt of federal research funding in the United States,[43] a requirement that holds equally for domestic research and research conducted in LMIC. Although some innovative training programs are emerging that focus on international research issues for U.S. investigators, most focus on the U.S. regulations and emphasize what investigators are required to do to be compliant with them. Programs that teach skills and strategies related to engagement and negotiation within the context of research ethics training have not yet emerged, but may be worthy of careful consideration. But whatever the status of existing programs, there is clearly an opportunity to enhance investigators' relevant skills in innovative ways and to design rigorous evaluations of such training that might help to gauge its impact on exploitation in LMIC.

CONCLUSION

Researchers applying the current international research ethics guidelines might represent a critical and under-appreciated human resource pool for improvements in global health. They are uniquely positioned to provide leadership in *engagement* with host country communities and the ensuing *negotiations* about the specific conditions under which the research will proceed, including the planned distribution of expected benefits. These social mechanisms are the means to fulfilling the current international research ethics guidelines related to prior agreements, capacity-building, and assurance of on-going access to beneficial interventions. The ethical end that they serve is the reduction of exploitation in international health research through fair distribution of its benefits in small-scale, as well as large-scale, studies. With improved training and supportive mechanisms, some evolution in the culture of research ethics review, and a serious effort to evaluate the impact of current international guidelines, these guidelines will not be the source of deleterious, pointless role expansion for investigators. Instead, they will contribute to an important end: The development of improvements in the

43. *See* NAT'L INSTS. OF HEALTH, REQUIRED EDUCATION IN THE PROTECTION OF HUMAN RESEARCH PARTICIPANTS (June 5, 2000), http://grants2.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

benefits to LMIC communities that participate in international collaborative research.