

What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical Research

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(See the editorial commentary by Kuritzkes, on pages 794–5.)

In recent years, there has been substantial debate about the ethics of research in developing countries [1–5]. In general, the controversies have centered on 3 issues: first, the standard of care that should be used in research in developing countries [6–13]; second, the “reasonable availability” of interventions that are proven to be useful during the course of research trials [14–19]; and third, the quality of informed consent. The persistence of controversies on such issues reflects, in part, the fact that existing ethical guidelines can be interpreted in multiple ways, are sometimes contradictory, or rely on unstated, yet controversial, ethical principles [6, 7, 9–11, 13, 20–24].

To provide unified and consistent ethical guidance, we apply a previously proposed ethical framework for clinical research within developed countries to developing countries, explicating a previously implicit requirement for collaboration [25]. More importantly, we propose specific and practical benchmarks to guide researchers and

research-ethics committees in assessing how well the enumerated ethical principles have been fulfilled in particular cases.

MINIMIZING EXPLOITATION

An ethical framework for multinational research should minimize the possibilities of exploitation [25]. A exploits B when B receives an unfair level of benefits or unfair burden of risks as a result of interacting with A [25, 26]. In developed countries, the risk of exploitation of subjects or host communities is minimized, because society funds research to improve health, researchers and research institutions are part of the larger community, and there is an infrastructure, even if imperfect, that translates research results into health-care practices for the benefit of the larger community. Research in developing countries creates a greater risk of exploitation: individuals or communities in developing countries assume the risks of research, but most of the benefits may accrue to people in developed countries [27]. Although poverty, limited health-care services, illiteracy, cultural and linguistic differences, and limited understanding of the nature of scientific research neither cause nor are necessary for exploitation, they increase the possibility of such exploitation [16–20, 26–28]. Furthermore, the regulatory infrastructures and independent oversight processes that might minimize the risk of exploitation

may be less well established, less supported financially, and less effective in developing countries. Guidelines for ethical research should minimize the risk of exploitation under these circumstances [28].

BEYOND PRINCIPLES TO BENCHMARKS

Previously, we delineated a framework for ethical research that included 7 principles [25]. However, an ethical framework for research in developing countries must provide more than broad principles. As Macklin notes, underlying the apparent “harmony [on principles] we confront unanswered questions, as well as stark disagreements” [29, page 19]. Accordingly, we add an eighth principle—collaborative partnership—and elaborate these principles through 31 benchmarks that systematically specify practical measures to determine the extent to which the research satisfies the principles (table 1) [30, 31].

This framework of principles and benchmarks is complex, because ethical evaluation of clinical research is complex. A single ethical principle is rarely absolute; most situations implicate multiple principles [32–34]. Consequently, the various principles and benchmarks will compete and must be balanced against each other—a process that inevitably requires judgment [30, 32–34].

Importantly, this framework functions

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Table 1. Ethical principles and benchmarks for multinational clinical research.

Principles	Benchmarks
Collaborative partnership	<p>Develop partnerships with researchers, makers of health policies, and the community.</p> <p>Involve partners in sharing responsibilities for determining the importance of health problem, assessing the value of research, planning, conducting, and overseeing research, and integrating research into the health-care system.</p> <p>Respect the community's values, culture, traditions, and social practices.</p> <p>Develop the capacity for researchers, makers of health policies, and the community to become full and equal partners in the research enterprise.</p> <p>Ensure that recruited participants and communities receive benefits from the conduct and results of research.</p> <p>Share fairly financial and other rewards of the research.</p>
Social value	<p>Specify the beneficiaries of the research—who.</p> <p>Assess the importance of the health problems being investigated and the prospective value of the research for each of the beneficiaries—what.</p> <p>Enhance the value of the research for each of the beneficiaries through dissemination of knowledge, product development, long-term research collaboration, and/or health system improvements.</p> <p>Prevent supplanting the extant health system infrastructure and services.</p>
Scientific validity	<p>Ensure that the scientific design of the research realizes social value for the primary beneficiaries of the research.</p> <p>Ensure that the scientific design realizes the scientific objectives while guaranteeing research participants the health-care interventions to which they are entitled.</p> <p>Ensure that the research study is feasible within the social, political, and cultural context or with sustainable improvements in the local health-care and physical infrastructure.</p>
Fair selection of study population	<p>Select the study population to ensure scientific validity of the research.</p> <p>Select the study population to minimize the risks of the research and enhance other principles, especially collaborative partnership and social value.</p> <p>Identify and protect vulnerable populations.</p>
Favorable risk-benefit ratio	<p>Assess the potential risks and benefits of the research to the study population in the context of its health risks.</p> <p>Assess the risk-benefit ratio by comparing the net risks of the research project with the potential benefits derived from collaborative partnership, social value, and respect for study populations.</p>
Independent review	<p>Ensure public accountability through reviews mandated by laws and regulations.</p> <p>Ensure public accountability through transparency and reviews by other international and nongovernmental bodies, as appropriate.</p> <p>Ensure independence and competence of the reviews.</p>
Informed consent	<p>Involve the community in establishing recruitment procedures and incentives.</p> <p>Disclose information in culturally and linguistically appropriate formats.</p> <p>Implement supplementary community and familial consent procedures where culturally appropriate.</p> <p>Obtain consent in culturally and linguistically appropriate formats.</p> <p>Ensure the freedom to refuse or withdraw.</p>
Respect for recruited participants and study communities	<p>Develop and implement procedures to protect the confidentiality of recruited and enrolled participants.</p> <p>Ensure that participants know they can withdraw without penalty.</p> <p>Provide enrolled participants with information that arises in the course of the research study.</p> <p>Monitor and develop interventions for medical conditions, including research-related injuries, for enrolled participants at least as good as existing local norms.</p> <p>Inform participants and the study community of the results of the research.</p>

within general ethical values, such as honesty, that are relevant to scientific integrity and avoidance of fraud [30, 31]. In addition, these principles and benchmarks must be specified before there can be any enforcement mechanism. We cannot determine how to enforce until we determine what to enforce.

COLLABORATIVE PARTNERSHIP

A collaborative partnership between researchers and sponsors in developed countries and researchers, policy makers, and communities in developing countries helps to minimize the possibility of exploitation by ensuring that a developing country determines for itself whether the research is acceptable and responsive to the community's health problems [28]. Moreover, without the engagement of researchers and host communities in the developing country, a study is unlikely to have any lasting impact, and, without the investment of makers of health policies, the research results are unlikely to influence policy making and the allocation of scarce health-care resources. A collaborative partnership also demonstrates awareness of and respect for cultural differences [35].

What constitutes a collaborative partnership? Six benchmarks seem to be essential (table 1). First, it requires partners—representation of parties in the developing country. Second, it requires collaboration—sharing responsibility for assessing the importance of the health problem and the value of the research to the community, for planning and conducting the study, disseminating the results, and ensuring that they are used for health improvements.

Third, a collaborative partnership requires mutual respect. This entails recognition of and respect for the host community's distinctive values, culture, and social practices, which should be incorporated into the design and implementation of the study. Importantly, respect does not

mean uncritical acceptance of practices that might be oppressive or coercive.

Fourth, a true collaborative partnership aspires to minimize disparities between researchers and sponsors from developed countries and the host community, at least disparities related to the research project. This could occur through development of health-care research resources and investment in the health-care sector, such as assistance with training of researchers and health-care workers, development and implementation of standard operating procedures for both clinical research and ethics review, and the establishment of a system for independent ethical review of research proposals.

Fifth, the community in which the research is being conducted should receive fair benefits from the conduct and/or results of the research [28]. Such benefits might include employment and training for community members to augment health-care services for the entire community [28]. Sixth, collaborative partnership requires a fair distribution of the tangible and intangible rewards of research among the partners. Very little can generate more resentment, mistrust, and a sense of exploitation than unfair distribution of the benefits of collaboration. This may require agreements on sharing intellectual property rights, royalties, and other sources of financial profit, as well as appropriate authorship and other credit for contributions to the research.

SOCIAL VALUE

It is widely recognized that ethical clinical research must have social value, through generation of knowledge that can lead to improvements in health; without social value, research exposes participants to risks for no good reason and wastes resources [25, 36]. However, the process of translating research results into health improvements is complex, incremental, and haphazard [37]. Typically, early studies are valuable only because the infor-

mation they generate informs additional research that cumulatively could change health care. Priorities may change while a study is being conducted, and the cooperation of diverse groups is often needed to make changes on the basis of research results. Consequently, determinations of social value are always uncertain and probabilistic, entailing judgments about the usefulness of a sequence of research [37]. Even in wealthy countries with well-established research and health-care infrastructures, research results are imperfectly incorporated into clinical practice. These problems are more complex in developing countries, where health-care infrastructures and funding are less well supported and developed. Consequently, the social value of research for the host community must be explicitly specified and enhanced.

Four benchmarks ensure social value. First, it should be determined who will benefit from the research. It is important to delineate the prospective beneficiaries of the research study, specifying whether they include the local community from which research participants will be enrolled, the host country, or people outside the host country.

Second, the potential value of the research for each of the prospective beneficiaries should be outlined. Each potential beneficiary may rank the health problem's importance differently. For example, because malaria is a substantially greater health problem for certain developing countries than for developed countries, improvements in interventions for cerebral malaria may be of substantial value to people in developing countries, whereas research on prophylactic medications for malaria will be more valuable for tourists from developed countries, and a malaria vaccine may be of substantial value to everyone.

Third, it is important to develop mechanisms to enhance the social value of research. Through collaborative partnerships, strategies should be devised to disseminate results in appropriate languages

and formats to key stakeholders, including the local community, health policy makers, health-care providers, and international health-care organizations. This may require not only presentations at scientific conferences and publications in journals but also novel forms of dissemination, such as presentations at community gatherings [35]. Social value can also be enhanced when research is integrated into a long-term collaborative strategy, so that the research project forms part of a more comprehensive research and health-care delivery strategy to address significant health problems.

Fourth, the conduct of the research should not undermine the community's existing health-care services. Beyond this minimal requirement, supplementing the existing system through the provision of additional resources, equipment, medications, or training appropriate to the research can enhance value.

SCIENTIFIC VALIDITY

Science and ethics do not conflict; valid science is an ethical requirement [25, 37]. Unless research generates reliable and valid data that can be interpreted and used by the specified beneficiaries of the research, it will have no social value, and participants will be exposed to risks for no benefits [25, 37]. In addition to the standard requirements for valid research, such as adequate sample size and unbiased measurement of outcome, multinational research should fulfill 3 benchmarks.

First, a research study must be designed so that the results will be useful in the context of the health problem in the developing country [29]. Interventions should be selected to ensure that the design is useful in identifying effective or appropriate interventions; implementing socially, culturally, and economically appropriate changes in the health-care system; or providing a reliable foundation for conducting subsequent research. Interventions are selected to ensure that the design will realize social

value and that the data are generalizable to the host community [38].

Second, the study design must realize the research objectives while neither denying health-care services that participants are otherwise entitled to nor requiring services that are not feasible to deliver in the context of the country's health-care system [10–12, 37, 39]. Determining entitlement to medical services in studies is challenging, because entitlements differ among countries [40, 41]. Even in wealthy countries, participants are not entitled to every available or effective medical service, because justice necessitates establishing priorities [41, 42]. For instance, it is widely accepted that cardiac research should not be required to include a coronary care unit, because participants would not be entitled to this service under a just distribution of resources [9, 10, 12, 43]. Conversely, in a study evaluating interventions to reduce mortality from cerebral malaria conducted in rural settings where travel to hospitals is impracticable, provision of bed nets may be part of a valid design, even if participants may not otherwise have them [44]. If the study's objective is deemed to be socially valuable, especially to the enrolled participants' community, demands for providing more-comprehensive interventions beyond those to which participants are entitled or beyond those that are feasible and sustainable may be unethical if they undermine the scientific objectives or make the results irrelevant to the community.

Third, the study must be designed to be feasible, given the social, political, and cultural environment in which it is being conducted [12]. Ensuring feasibility might require sustainable improvements to the health-care infrastructure, such as training of personnel, construction of additional facilities, or provision of an affordable drug.

FAIR SUBJECT SELECTION

Historically, populations that were poor, uneducated, or powerless to defend their

own interests were targeted for high-risk research, whereas promising research was preferentially offered to more-privileged individuals [25]. A challenge for research in developing countries is fair selection of target villages, tribes, or city neighborhoods from which individual participants will be recruited. First, at a minimum, the study population should be selected to ensure valid science [25]. Scientific reasons for choosing a particular community might be high prevalence, incidence, or transmission rates of an infection, special drug-resistance patterns, or particular combinations of diseases.

Scientific considerations alone will usually under-determine which community or individuals are selected. Second, minimizing risk is essential. For instance, in selecting a target population for an HIV vaccine study, a community that does not discriminate against HIV-infected persons and that can provide treatment for opportunistic infections is preferable. Third, the community should be one in which a collaborative partnership can be developed and in which social value can be realized. Consequently, it is preferable to select communities that have established or that are capable of establishing a system for identifying legitimate representatives and that will share responsibility for planning and conducting the study and ensuring that results are implemented through health system improvements or additional research.

Fourth, factors such as familial coercion, social marginalization, political powerlessness, and economic deprivation must be considered, to determine the vulnerability of communities or groups within the community [45]. For instance, if health policy makers suggest a particular tribe, the researchers should determine that the group has been selected for good reasons, such as a high incidence of disease, not because of social subjugation. If a scientifically appropriate population is identified as vulnerable, specific safeguards to protect the population should be imple-

mented, such as ensuring confidentiality and the freedom of potential research participants to decline joining the study.

FAVORABLE RISK-BENEFIT RATIO

All clinical research should offer participants a favorable risk-benefit ratio, or, if potential risks outweigh benefits to participants, the social value must justify these risks [25, 46]. Only benefits that accrue to participants from the interventions necessary to achieve the research objectives or those deriving from the knowledge to be gained by the research should be used to justify risks to participants [25, 47].

Two benchmarks unique to developing countries apply. First, the risk-benefit ratio for individuals must be favorable in the context in which they live. The underlying risks of a particular disease can vary because of differences in incidence, drug resistance, genetic susceptibility, or social or environmental factors. When participants confront a higher risk of disease, greater potential benefits may justify greater risks in research design [48]. Similarly, the risk-benefit ratio for a particular study may be favorable in communities where the social value of the research is high but may be unfavorable where potential value is lower [25, 51].

Second, the risk-benefit ratio for the community should also be favorable. To make this assessment, the risks and potential benefits for the community, such as increased antibiotic resistance or collection of sensitive information, must be specified. Benefits might include the information obtained from the study, services provided to participants, or improvements in the health of the community. Furthermore, to be consistent with collaborative partnership, the community should determine whether the risks are acceptable in light of the benefits to be derived from the conduct and results of the research [28, 35]. This decision should be confirmed by people familiar with other studies.

INDEPENDENT REVIEW

To minimize concerns with regard to researchers' conflicts of interest and to ensure public accountability, independent ethical review of all clinical research protocols is necessary [25]. In addition to institutional review board or research ethics committee review, other regulatory approvals may be necessary for some types of research.

In multinational research, there is a special need for transparency [28]. Transparency enhances accountability by assuring the public that the research is not exploitative. Whether supplementary reviews by local community councils, nongovernmental organizations involved with the community, international health organizations, or ministries of health are appropriate depends on the nature of the collaborative partnership. If such reviews are in disagreement, it is important to clarify the nature of the disagreement. In many cases, disagreement reflects different ways of balancing various principles and benchmarks or the appropriateness of different ways of fulfilling them—that is, not whether the ethical requirements are met, but how they are met [49]. Conflicts may also arise because of different guidelines or regulatory requirements, which themselves may not have good ethical justification or may be insensitive to particular cultural or social circumstances in developing countries [14, 50]. Only rarely are there fundamental disagreements about whether ethical principles and benchmarks are met. Unfortunately, there is no widely accepted procedure for adjudicating such conflicts. In practice, the requirements specified by the review board in the sponsor's country are often determinative, which contravenes the principle of collaborative partnership [51].

Finally, review must be independent and competent [25]. Review bodies may have conflicts because of relationships with the researchers or pressures from those promoting the research. Supplementary training in ethics for review bodies may be necessary.

INFORMED CONSENT

Individual informed consent has been recognized as a principle of ethical clinical research for more than a century [52, 53]. Differences in language, social traditions, and practices make the process of informed consent in developing countries complex and suggest 5 benchmarks for evaluating informed consent. First, the local community should help to establish recruitment procedures and incentives for participants that are consistent with cultural, political, and social practices. In some communities, compensation for participation in research may be expected, whereas, in others, it may be considered offensive. The appropriate form and level of compensation depends on the local economic and social context. Although concerns about inducement are frequently raised, high potential social value and a favorable risk-benefit ratio dispel these concerns [54, 55]. Indeed, focusing on undue inducement could reduce compensation and some of the benefits for subjects and host communities. Paradoxically, balancing fair compensation and undue inducement may result in less compensation for members of impoverished communities.

Second, disclosure of information should be sensitive to the local context. It should be done using the local language, culturally appropriate idioms, and analogies that the prospective participants can understand. This obviously entails a need for collaborative partnership.

Third, "spheres of consent," ranging from village elders to leaders of the extended family or heads of households, may be required before researchers can invite individual participation [35]. With few exceptions, such as emergency research, it is unacceptable to supplant individual consent of adults by family or community consent [35, 56]. The family or community only gives permission to invite individuals to participate.

Fourth, researchers should use consent procedures that are acceptable within the local community, while ensuring that an independent observer could verify volun-

tary participation by the individuals. For instance, US regulations requiring a written signature are culturally insensitive in many cases [53, 57]. Appropriate alternative procedures for documenting informed consent might include tape recordings or written documentation of verbal consent.

Fifth, special attention must be given to ensure that individuals are aware of their right to and actually are free to refuse to participate or withdraw from research [58]. To obviate familial or community coercion or retribution, steps such as prorating compensation and other benefits related to the research should be taken.

RESPECT FOR RECRUITED PARTICIPANTS AND STUDY COMMUNITIES

The ethical conduct of clinical research does not end when informed consent is obtained [25]. Researchers have ongoing obligations to participants, former participants, and the host community. First, an essential obligation is to develop and implement procedures to maintain the confidentiality of information collected. Such procedures might include interviewing participants outside, where they cannot be overheard, or permitting participants to not receive HIV test results. In addition, it is important to alert participants that, despite researchers' best efforts, there is no guarantee of absolute confidentiality.

Second, respect for participants includes informing them of their right to withdraw [58]. Third, participants and the community should be informed when new information, such as a newly discovered risk, arises during the course of research. Fourth, exacerbations of the disease being studied, adverse events from research interventions, and health problems that arise unrelated to the disease being studied may require care. Researchers should specify a strategy for monitoring the progress of the disease, adverse events from the intervention, any untoward changes in health, what steps will be

taken to provide care under these circumstances, and what compensation there will be for research-related injuries.

One problematic area with regard to research in developing countries is the responsibility of researchers for participants' health problems that are unrelated to the condition being studied. In developed countries, researchers commonly refer participants to the existing health-care system, notwithstanding deficiencies in insurance coverage and provision of care. In developing countries, geography and scarce resources may make treatment for diseases unrelated to the research unavailable. Currently, there are no clearly defined parameters to guide researchers in these situations. Clinical research is not clinical care [59]. Researchers are not obligated to remedy the deficits of a country's health-care system or to ensure that all participants' medical ailments are given appropriate care. Conversely, researchers cannot ignore concomitant health problems of their participants. At a minimum, researchers should ensure access to local health services or alternatives of equal quality and meet national care guidelines when specified, such as for childhood immunizations. In some cases, researchers may provide interventions for unrelated health conditions that are superior to those locally available, especially if they are relatively easy and economical to provide under local conditions. It is important that plans for provision of care of unrelated health conditions be developed as part of the collaborative partnership between researchers, the host community, and makers of health policies.

What medical services should be provided to research participants after completion of the study? Some have argued that interventions proven to be beneficial to participants during a study should be made available to them at the completion of the study [13, 60]. Continued access to experimental medications is one way in which subjects may benefit from research participation [28]. However, participation in research does not necessarily entitle

subjects to continue receiving treatment, nor does it obligate investigators to provide continued treatment; to do so would be to confuse research with clinical care.

Finally, researchers should develop explicit strategies to inform participants and host communities of the results of the research [35]. Having participated in the research and assumed risks, the participants and host community have a right to know what was found and its implications for public health and health-care policies.

APPLYING THE PRINCIPLES AND BENCHMARKS

Together, these principles and benchmarks constitute a systematic framework that specifies core practical considerations necessary to ethically justify research in developing countries. It can probably be applied to all research, regardless of setting or sponsorship. This is a first attempt to specify a comprehensive list of benchmarks. Application to actual research studies may suggest refinement or the need for additional benchmarks [30, 41].

Importantly, differences in health, economic, social, and cultural aspects of a research setting will affect application of the framework—specifically, how much “weight or priority [is] given to different benchmarks” [30, page 740]. Depending on a study's objectives and context, particular benchmarks will be given greater weight than others. Such balancing is inevitable whenever there are multiple ethical considerations [32–34]. This does not mean that the principles and benchmarks are relativistic; rather, it means that the adaptation and balancing of universal principles are relative to risk, resources, social practices, and similar circumstances.

Moral arguments take place in context, and they therefore depend at least implicitly on matters of fact, estimates of risk, suppositions about feasibility, and beliefs about human nature and social processes.... Even those who rely on what they regard as universal moral principles do not presume

that their practical conclusions are independent of reliable facts and plausible assumptions about particular societies. The arguments begin from where we are, and appeal to those with whom we now live. This is why moral relativism is seldom as important an issue in practical as it is in theoretical ethics. [61, page 14–15]

OBJECTIONS CONSIDERED

The first objection to consider is that this framework is overwhelming, erecting barriers to research in developing countries. However, it does not add ethical requirements; rather, it provides an explicit and systematic delineation of steps already being taken by conscientious researchers in developing countries.

Second, it may be claimed that these principles and benchmarks are obvious and do not add to existing guidance. Indeed, the principles are distilled and made coherent from widely accepted guidance, including the Nuremberg Code [22], the Declaration of Helsinki [13], the Belmont Report [24], or the US “Common Rule” [58]. The benchmarks provide more-specific and more-practical guidance: a set of measures that can serve as a reminder and common reference for all those planning, conducting, and evaluating research. Such obviousness constitutes a virtue. Agreement on the benchmarks would indicate that consensus on the broad principles could be extended to ever more-specific and more-substantive aspects of the ethical framework, narrowing the disagreement that Macklin justifiably laments [29].

Third, disagreement is inevitable [29]. We agree. Consideration of multiple ethical principles and benchmarks simultaneously is likely to create reasonable disagreement [32–34]. However, these benchmarks can both narrow the disagreements and make them less ethically worrisome. Ignoring basic principles or rejecting the benchmarks in designing and conducting a research study could render a study unethical. Conversely, accepting the principles and

benchmarks, yet disagreeing about how to balance them in a particular case, highlights the intricacies of ethical judgments entailing multiple considerations [61]. Disagreement on the balancing of the various benchmarks does not necessarily make one assessment ethical and the other unethical. Rather, it may reflect different but legitimate ways of resolving competing ethical claims. In fact, this framework can help narrow disagreements and elucidate the different underlying views. Ultimately, in the effort to ensure that research is conducted ethically, a thoughtful process of balancing ethical considerations can be as important as any particular judgment.

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