

The Oxford Textbook of Clinical Research Ethics

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An Ethical Framework for Biomedical Research

Over the last 60 years or so, there has been myriad guidance on the ethical conduct of research with humans¹⁻¹³ (see Table 11.1). Despite the profusion, the extant guidance seems flawed in several respects. First, most guidance was “born in scandal.”¹⁴ That is, the guidelines or reports were a response to a specific controversy, and therefore tend to focus on what was perceived to be the transgression of that scandal. The Nuremberg Code directly addressed the atrocities of the Nazi physicians;² the Belmont Report was a response to the Tuskegee Syphilis Study and other scandals;⁴ and the Advisory Committee on Human Radiation Experiments responded to covert radiation experiments during the Cold War and therefore emphasized deception.¹⁵ Second, regulatory guidance tends not to examine the overall ethics of research but to have a specific practical purpose. For instance, the International Conference on Harmonisation has the purpose of creating common rules across developed countries for the “registration of pharmaceuticals for human use.”⁸ The aim is more to enhance the efficiency of drug approval than to protect research participants, for which it defers to the Declaration of Helsinki.³ In general, these regulatory guidelines emphasize the procedural safeguards of informed consent and independent review by an institutional review board or research ethics committee because these leave “paper trails” that can subsequently be audited.

Both of these deficiencies contribute to a third: existing guidance is neither comprehensive nor systematic. The guidelines tend to be lists of claims or principles. For instance, the Nuremberg Code with its 10 statements and the Declaration of Helsinki, originally with 22 principles subsequently expanded to 32, contain no elaboration.^{2,3} Such sparse, oracular statements lack an overarching framework to ensure that all relevant ethical issues are

addressed. They also lack justifications for their claims, implying that the ethical guidance is either self-evident or beyond debate. Consequently, when controversies arise about whether the principle itself is valid or how a principle should be applied to a case, there is nothing to appeal to other than the authority of these documents. Agreement can frequently be secured on the broad principles, but this often hides deep disagreements about how they should be interpreted and applied to specific situations.¹⁶

Finally, and maybe most important, the existing guidance seems mistaken on some important issues. For instance, the Nuremberg Code’s strong statement that “the voluntary consent of the human subject is absolutely essential” seems to prohibit all pediatric research.² Yet this seems wrong. Similarly, the 1993 Council for International Organizations of Medical Sciences (CIOMS) guidelines recommended that Phase I or II studies of drugs and vaccines should be conducted first in sponsoring countries before being done in developing countries.¹⁷ Because of strong objections, especially by developing countries, a decade later this was deleted from the revision.⁶ The most recent version of the Declaration of Helsinki addresses conflicts of interest through disclosure, requiring that potential research participants be adequately informed about “any possible conflict of interest” and that these “should be declared in the publication.”³ The value and importance of disclosing conflicts of interest to research participants is controversial.¹⁸ More important, exclusive reliance on disclosure in the absence of prohibitions on certain conflicts of interest seems inadequate.^{19,20}

Because of the deficiencies of existing research ethics guidance, there is a need for a broader, systematic, and comprehensive framework that includes an ethical justification and specification

Table 11.1
Selected Guidelines on the Ethics of Biomedical Research With Humans

Guideline	Source	Year Issued, Revised, or Amended	Chapter and Reference
Nuremberg Code	Nuremberg Military Tribunal decision in <i>United States v. Brandt et al.</i>	1947	Chapter 12 http://www.hhs.gov/ohrp/references/nurcode.htm
Declaration of Helsinki	World Medical Association	1964; revised: 1975, 1983, 1989, 1996, 2000; amended: 2002, 2004	Chapter 13 http://www.wma.net/e/policy/b3.htm
Belmont Report	National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research	1979	Chapter 14 http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm
45 CFR 46 (Common Rule)	U.S. Department of Health and Human Services (DHHS) and 16 other U.S. federal agencies	DHHS guidelines: 1981 Common Rule: 1991	Chapter 16 http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm
International Ethical Guidelines for Biomedical Research Involving Human Subjects	Council for International Organizations of Medical Sciences in collaboration with World Health Organization	1982 [draft]; revised: 1993, 2002	Chapter 15 http://www.cioms.ch/frame_guidelines_nov_2002.htm
Good Clinical Practice: Consolidated Guidance	International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use	1996	http://www.fda.gov/cder/guidance/959fnl.pdf
Resolution 196/96: Rules on Research Involving Human Subjects	National Health Council, Brazil	1996	
Convention on Human Rights and Biomedicine	Council of Europe	1997; revised: 2005	Chapter 17 http://conventions.coe.int/treaty/en/treaties/html/164.htm [1997]; http://conventions.coe.int/treaty/en/treaties/html/195.htm [2005]
Medical Research Council Guidelines for Good Clinical Practice in Clinical Trials	United Kingdom	1998	http://www.mrc.ac.uk/pdf-ctg.pdf
Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda	Uganda National Council for Science and Technology	1998	
Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans	Tri-Council Working Group, Canada	1998; amended: 2000, 2002, 2005	http://www.pre.ethics.gc.ca/english/policystatement/policystatement.cfm
National Statement on Ethical Conduct in Research Involving Humans	National Health and Medical Research Council, Australia	1999	http://www.nhmrc.gov.au/publications/_files/e35.pdf
Ethical Guidelines for Biomedical Research on Human Subjects	Indian Council on Medical Research, New Delhi	2000	http://www.icmr.nic.in/bioethics.htm
Guidelines on Ethics for Health Research in Tanzania	Tanzania National Health Research Forum	2001	
Guidelines on Ethics in Medical Research: General Principles	Medical Research Council of South Africa	1977; revised: 1987, 1993, 2002	http://www.sahealthinfo.org/ethics/ethicsbook1.pdf
Guidelines for Good Clinical Practice in the Conduct of Clinical Trials in Human Participants in South Africa	Department of Health, South Africa	2000	http://www.doh.gov.za/docs/index.html

for how each principle is to be fulfilled in practice.^{21,22} Among other goals, this framework should incorporate those concerns that overlap in the existing guidance and organize them into a coherent whole.

Fundamental Ethical Purpose

Informing this overarching framework is the understanding that the fundamental ethical challenge of all research with humans is to avoid exploitation.^{21,22} Research aims at obtaining generalizable knowledge that can be used to improve health and health care. Participants in research are a necessary means to obtaining this knowledge. Consequently, participants are used in the research process for the benefit of others and are at risk of being exploited. The fundamental purpose of research guidelines is to minimize the possibility of exploitation in clinical research.

There are two distinct conceptions of exploitation. Both are important in protecting research participants. One is the traditional, Kantian notion of exploitation as using an individual merely as a means and not simultaneously as an end in itself.^{23,24} This Kantian conception of exploitation is grounded in the use of individuals for an end they do not agree with or to which they have not consented. Using individuals without their consent violates their autonomy.²⁵ The remedy for the Kantian type of exploitation is obtaining informed consent and sometimes ensuring collaborative partnership with a larger community that agrees to the research.

A second conception of exploitation elaborated by Alan Wertheimer rests on the unfair distribution of the benefits and burdens of an interaction.^{26,27} This is distinct from the Kantian conception because it concerns the distribution of benefits—who benefits and how much they benefit—rather than autonomy. Importantly, this type of exploitation can occur even when the interacting parties provide valid consent.²⁶ Minimizing this type of exploitation is more complex, requiring the fulfillment of multiple principles.²⁷

Principles and Benchmarks of Ethical Clinical Research

The following eight ethical principles provide a comprehensive and systematic framework to guide the ethical conduct of clinical research and thereby minimize the possibility of exploitation^{21,22} (see Table 11.2). These principles are general and identify considerations necessary to justify research as ethical. They are conceptually included in most of the previously mentioned guidance, although existing guidelines do not necessarily include all of them. In addition, they are presented sequentially, going from the development of research proposals to the conduct of research to monitoring during research.

Each principle is specified by benchmarks that offer a specific elaboration and understanding of each principle.²² The benchmarks are practical interpretations of what is required to fulfill each principle.^{22,28,29} In this sense, the benchmarks should clarify and focus the kinds of values and considerations at stake in fulfilling each principle. No matter how specific and detailed, the benchmarks cannot eliminate all controversy over the principles.^{16,22} However, by specifying and clarifying the eight princi-

ples, these benchmarks should help to narrow any disagreement related to specific cases, making it easier to focus on the substance of the disagreement, assess the importance of the problems and concerns, and even identify potential solutions.²²

Collaborative Partnership

Clinical research is meant to serve a social good, to enhance the health and health care of people. It is part of the way people collectively improve their well-being. Clinical research is not meant to be done *to* people but done *with* people.³⁰ The principle of collaborative partnership recognizes that the community in which research is conducted should collaborate in the research endeavor.^{22,27} Seeking the community's agreement and input helps ensure that the particular community will not be exploited.²⁷ In addition, collaboration helps ensure—although it does not guarantee—that the community will receive fair benefits from the conduct of the research.^{27,31} Collaborative partnership helps ensure that the community determines for itself whether the research is acceptable and responsive to its health problems. Finally, collaborative partnership is practically important. Without the engagement of researchers and community members, research is unlikely to have any lasting impact. Without the investment of health policy makers, the research results are unlikely to influence policy making and the allocation of scarce health-care resources.²²

Collaborative partnership can be fulfilled through myriad formal and informal mechanisms. For instance, establishment of community advisory boards, consultations with advocacy groups, public meetings with community members, and advocacy for funding of research are approaches to developing collaborative partnerships.^{30,32} Which method is preferred depends upon the nature of the particular research study. Because many of these mechanisms exist in the background without the need to launch explicit initiatives or are just part of “doing business,” collaborative partnership has infrequently been included as an explicit ethical requirement of clinical research.²¹ One example of research that fails on collaborative partnership grounds includes “helicopter research” in which researchers arrive in a community, take samples, and leave, never to return.

Several benchmarks are essential to fulfilling the principle of collaborative partnership.²² First, collaborative partnership obviously requires partners. This means identifying representatives of the target community to be involved in the research. Second, it requires collaboration. This entails sharing responsibility for assessing the importance of the health problem and the value of the research to the community, as well as for planning and conducting the study, disseminating the results, and ensuring that the results are used for health improvements.

Third, a collaborative partnership requires mutual respect. This entails recognition of and respect for a community's distinctive values, circumstances, culture, and social practices.³⁰ Importantly, respect does not mean uncritical acceptance of practices that might be oppressive or coercive. Indeed, some of these practices may be challenged in research. A true collaborative partnership based on respect also aspires toward equality between the partners. In this sense, collaborative partnership aspires to minimize the deprived circumstances of the involved community. Research aims to ameliorate deprivations usually of disease and sometimes of social circumstances. This could occur through a number of interventions directly related to the goals of the research

Table 11.2
Principles and Benchmarks for Ethical Clinical Research

<i>Principles</i>	<i>Benchmarks</i>
Collaborative partnership	<ul style="list-style-type: none"> • Which community representatives will be partners, involved in helping to plan and conduct the research, disseminate the results and use the results to improve health? • How will responsibility be shared with these partners for planning and conducting the research, disseminating the results and using the results to improve health? • How will respect for the community's values, circumstances, culture, social practices, and so forth, be demonstrated? • How will fair benefits for the community from the conduct and results of the research be assured? • How will the tangible benefits of the research, such as authorship credit and intellectual property rights, be distributed to ensure fairness?
Social value	<ul style="list-style-type: none"> • Who will benefit from the conduct and results of research? • What is the potential value of the research for each of the prospective beneficiaries? • How will the social value of the research be enhanced? • How can adverse impacts, if any, of conducting the research be minimized?
Scientific validity	<ul style="list-style-type: none"> • Do the scientific and statistical design and methods satisfy generally accepted standards and achieve the objectives of the study? If not, is there clear justification for the deviations? • Will the research results be interpretable and useful in the context of the health problem? • Does the study design ensure participants health-care services they are entitled to? If not, are there methodologically compelling reasons and are participants protected from serious harm? • Is the research design practically feasible given the social, political, economic, and cultural environment?
Fair participant selection	<ul style="list-style-type: none"> • Is the research population selected to ensure that the research complies with scientific norms and will generate valid and reliable data? • Is the research population selected to minimize risks to the participants? • Are the individual research participants selected to maximize social value and enhance the possibility of benefits to the participants? • Are the participants vulnerable based on age, clinical status, social marginalization, economic deprivation, and so forth? If so, what safeguards are included to protect the participants?
Favorable risk-benefit ratio	<ul style="list-style-type: none"> • Are the potential physical, psychological, social, and economic risks of the research for the individual participants delineated and their probability and magnitude quantified to the extent possible given the available data? • Are the potential physical, psychological, social, and economic benefits of the research for the individual participants delineated and their probability and magnitude quantified to the extent possible given the available data? • When compared, do the potential benefits to the individual participants outweigh the risks? If not, does the knowledge gained from the study for society justify the net risks to the individual participants?
Independent review	<ul style="list-style-type: none"> • Are the procedures for independent review established by law and regulation being properly followed? • Is the review body both independent and competent? • Is the review process transparent, and are reasons given for the review committee's decisions? • Are multiple reviews minimized and reconciled if they conflict?
Informed consent	<ul style="list-style-type: none"> • Are recruitment procedures and incentives consistent with cultural, political and social practices of the potential participants and their community? • Are disclosure forms and verbal disclosure procedures sensitive to participants' culture, language, and context? • Is the information presented to participants complete, accurate, and not overwhelming? • Are there appropriate plans in place for obtaining permission from legally authorized representatives for individuals unable to consent for themselves? • Are supplementary consents or permissions, for example, from spouses or community leaders, obtained? If so, are there ways to ensure that the individual participant can still decide whether to participate independent of the spouse or community leader? • Are the mechanisms to symbolize consent consistent with participants' culture and context? • How will individual participants be made aware of their right to refuse to participate and are they actually be free to refuse?
Respect for participants	<ul style="list-style-type: none"> • How will the health and well-being of participants be monitored to minimize harms? Are the criteria for changing doses or procedures for stopping the study for the health of participants adequate? • How will the confidentiality procedures actually be implemented? • How will it be ensured that participants who want to withdraw can withdraw without penalty? • How will results of the research be disseminated? • What are the plans for care of the participants after the research is completed?

project or ancillary mechanisms such as developing the general infrastructure necessary to actually conducting ethical research.

Fourth, the community in which the research is being conducted should receive fair benefits from the conduct and/or results of the research.^{27,31} What level of benefits is fair depends upon the burdens the community bears for the conduct of the research.²⁶ Such benefits might include direct benefits to the research participants as well as more indirect benefits such as employment and training for community members to augment health care services for the entire community.^{27,31}

Finally, 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 sense of exploitation than an unfair distribution of the benefits of collaboration. This may require agreements regarding sharing intellectual property rights, royalties, and other sources of financial profit as well as appropriate authorship and other credit for contributions to the research.^{27,31}

Social Value

Clinical research is not an end in itself. It has instrumental value because it generates knowledge that leads to improvement in health or health care.^{33,34} It is such improvements in health that ultimately constitute the social value of research. Unfortunately, the emphasis on protection of research participants has displaced the importance of assessing research's social value. Without social value, research exposes participants to risks for no good reason and wastes resources.^{21,22,33-35} However, the process of translating research results into health improvements is complex, incremental, and haphazard.³⁶ Typically, early studies are valuable because the data they generate informs additional research that ultimately could improve health. Priorities may change while a study is being conducted, and the cooperation of diverse groups is often needed to make changes based on research results. This makes the process of going from research to health improvement uncertain and arduous. Assessment of the value of research is made prospectively before any data are collected. Consequently, determinations of social value are uncertain and probabilistic, entailing judgments about the usefulness of a sequence of research and chances of implementing the results.^{35,36} Even in wealthy countries with well-established research studies and health system infrastructures, research results are imperfectly incorporated into clinical practice.

Certain kinds of research clearly lack social value: for example, research that is nongeneralizable, that addresses a problem of little relevance to anyone, that will not enroll sufficient numbers of patients, that assesses proven or empirically well-established results, and research that could never be practically implemented to improve health or health care even if effective in the research setting.^{37,38}

Consideration of four benchmarks helps to ensure fulfillment of the principle of social value.^{21,22} First, to whom will the research be valuable? It is important to delineate both the short-term and long-term prospective beneficiaries of the research study, specifying whether they include a specific group, similarly situated groups, a larger community from which research participants will be recruited, the country hosting the research, or people outside the host country.²²

Second, what is the potential value of the research for each of the prospective beneficiaries? Potential beneficiaries may rank the health problem's importance differently and may receive different benefits from the research results. Factors to be considered might include how widespread the disease or condition is, the impact of the disease on individuals and communities, and the extent to which the research is likely to offer an intervention or information useful to the beneficiaries. For example, because malaria is a substantially greater health problem for certain developing countries than for developed countries, research on cerebral malaria may be of substantial value to people in developing countries. Conversely, research on prophylactic medications for malaria is likely to be more valuable for tourists, whereas research on a malaria vaccine may be perceived as valuable to everyone, but to a different degree. Similarly, research on new HIV/AIDS medications in a developing country, although needed in that country, could benefit those outside the host country more than the community in which the research is being conducted if the ultimate cost of the medication is high.

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 ways to key stakeholders including people with the disease, practicing clinicians, advocacy groups, health policy makers, and sometimes international health-care organizations.^{22,30} In addition to presentations at scientific conferences and journal publications, this may require novel forms of dissemination such as letters to patients, articles in advocacy publications, presentations at community gatherings, public service announcements in the media, or letters to clinicians. Social value can also be enhanced when research is integrated into a long-term collaborative strategy, so that one research project forms part of a more comprehensive research and health delivery strategy to address significant health problems.²⁷

Finally, consideration should be given to the impact of the research on the existing health-care infrastructure. The conduct of the research should not undermine a community's existing health-care services or social structures and leave it worse off at the end of the research. Supplementing the existing system and contributing to sustainable improvements in health through the provision of additional resources, equipment, medications, or training appropriate to the research can enhance value.

Scientific Validity

Contrary to many claims, in research, science and ethics do not conflict.^{21,22,34} Valid science is a fundamental ethical requirement.^{21,22,35} 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 may be exposed to risks for no benefits.^{39,40} Research must be designed in a way that provides valid and reliable data.

Four benchmarks are important in fulfilling the principle of scientific validity. First, the scientific and statistical design and methods of the research must plausibly realize the objectives of the research and must also satisfy the generally accepted norms of research. Research must have clear, justifiable objectives, an adequate sample size, and unbiased and reliable outcome measures and statistical analyses. Deviations from such standards, such as innovative designs, must be plausibly justifiable to the research community.

Second, a research study must be designed to generate results that will be interpretable and useful in the context of the health problem.¹⁵ Interventions should be selected to ensure that the design is useful in identifying ineffective 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 should be selected to ensure that the design will realize social value and that the data are generalizable.^{21,22,41}

Third, 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.^{37,38,42} However, studies can be ethically designed yet not provide a service or intervention individuals are entitled to under certain, restrictive conditions.^{41,43-45} Specifically, it is ethical to use placebo or less than the diagnostic tests or treatments to which individuals are entitled when two conditions are fulfilled: (1) there is a methodologically compelling reason to do so, and (2) there is only minimal chance of serious harm—such as suffering irreversible morbidity or disability, or reversible but serious injury.^{41,43-45}

Determining entitlement to medical services in studies is challenging because entitlements differ among countries, and may differ among groups within a country.^{46,47} Even in wealthy countries, participants are not entitled to every available or effective medical service, because justice necessitates establishing priorities for the distribution of scarce resources.^{46,48} For instance, some developed countries may not guarantee expensive drugs when inexpensive but more inconvenient yet effective drugs are available. Similarly, it is widely accepted that cardiac research conducted in developing countries need not be designed to require a coronary care unit because participants would not necessarily be entitled to this service under a just distribution of scarce resources in those countries.^{37,38,42,46,49} Conversely, in a study evaluating interventions to reduce mortality from cerebral malaria conducted in rural settings in which travel to hospitals is impracticable, provision of bed nets may be part of a valid design even if participants may not otherwise have them.⁵⁰ However, even if the study's objective is deemed socially valuable, especially to the enrolled participants' community, it is not ethically necessary to provide more comprehensive interventions beyond those to which participants are entitled, especially interventions that may not be feasible and sustainable. Doing so may even be unethical if it undermines the scientific objectives or makes the results irrelevant to the enrolled participants' community.

Finally, the study must be designed in a way that is practically feasible given the social, political, and cultural environment in which it is being conducted.⁵¹ Ensuring feasibility might require extensive community education and outreach as well as sustainable improvements to the health-care infrastructure, such as training of personnel, construction of additional facilities, or provision of an affordable drug. Feasibility also requires that it be possible to achieve the sample size in a reasonable time frame.

Fair Participant Selection

Historically, populations that were poor, uneducated, or powerless to defend their own interests were targeted for high-risk re-

search, whereas promising research was offered to more privileged individuals.^{15,34,52} Fair selection of participants requires that the research objectives be the primary basis for determining eligibility.^{4,15,21,22,34} Once a target group is identified based on scientific objectives, considerations of minimizing risk, enhancing benefits, minimizing vulnerability, feasibility, as well as facilitating collaborative partnership, become determinative.²² Factors extraneous to the objectives, risks, benefits, and feasibility of conducting the research should not be the basis for selecting target communities or excluding individuals or communities.^{4,15,22,34}

Four benchmarks are necessary to fulfill the principle of fair participant selection. First, the study population should be selected to ensure valid science.^{21,22,34,53} Scientific reasons for choosing a particular group of individuals or a community might be high prevalence or incidence of a disease, the magnitude of harms caused by the disease, high transmission rates of an infection, special drug resistance patterns, deprived social circumstances that increase susceptibility to a disease, or particular combinations of diseases. Social status that is irrelevant to the research objectives should not influence selection. Scientific considerations alone, however, will usually underdetermine which community or individuals are selected.

Second, selecting participants in a way that minimizes risk is essential.⁵⁴ For instance, in selecting a target population for an HIV vaccine study, the extent to which a community protects HIV-infected persons against discrimination and provides treatment for opportunistic infections are important considerations to minimize risk. Similarly, individuals with high creatinine clearance may be appropriately excluded from a trial of a potentially renal toxic drug in order to reduce risk.

Third, individuals should be selected in order to enhance both the social value of the research and the possibility of benefits to participants.^{22,55-57} For example, assuring an adequate number of women in a study of a disease largely affecting women enhances benefits to women. Selecting individuals who are able to comply with the study's requirements will enhance the chances that they will benefit from the intervention and that the study will yield valid data. Communities should be selected 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, or can establish, 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.

Finally, factors such as cognitive ability, age, clinical status, familial relationships, social marginalization, political powerlessness, and economic deprivation should be considered in order to determine the vulnerability of individuals or groups.⁵⁸ For instance, if health policy makers suggest a particular group for research participation, the researchers should determine whether the group has been selected for good reasons, such as a high incidence of disease, or because of social subjugation. If scientifically appropriate individuals or groups are identified as vulnerable, specific safeguards to protect the population should be implemented, such as consent monitoring or independent capacity assessment, independent clinical monitoring, ensuring confidentiality, and ensuring that potential research participants are free to decline joining the study.

Favorable Risk-Benefit Ratio

Like life itself, all research entails some risks. However, clinical research typically should offer individual participants a favorable net risk-benefit ratio.^{21,22,34} In cases in which potential risks outweigh benefits to individual participants, the social value of the study must be sufficient to justify these net risks.^{4,59} Because clinical research involves drugs, devices, and procedures about which there is limited knowledge, uncertainty about the degree of risks and benefits is inherent. And the uncertainty is greater in early phase research.

The principle of a favorable net risk-benefit ratio requires fulfilling three benchmarks. First, the risks of the research should be delineated and minimized. Researchers should identify the type, probability, and magnitude of the risks of the research. The risks are not limited to physical risks, but should also encompass potential psychological, social, and economic risks. To the extent possible, the assessment of risks should be based on available empirical data, not intuition or speculation. Within the context of good clinical practice, these risks should be minimized "by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes."⁵ In addition, research procedures should be performed by trained and competent individuals who adhere to the standards of clinical practice.³

Second, the type, probability, and magnitude of the benefits of the research should be identified. The benefits to individual participants, such as health improvements, are relevant. The specification of potential benefits to individual participants should consider only health-related potential benefits derived from the research intervention itself.^{21,22,34} The benefits to society through the generation of knowledge are assumed if the research is deemed to be of social value and scientifically valid. Secondary benefits, such as payment, or adjunct medical services, such as the possibility of receiving a hepatitis vaccine not related to the research, should *not* be considered in the risk-benefit evaluation; otherwise simply increasing payment or adding more unrelated services could allow the benefits to justify even the riskiest research.^{22,60} Furthermore, although participants in clinical research often receive some health services and benefits, the purpose of clinical research is not the provision of health services. Services directly related to clinical research are necessary to ensure scientific validity and to protect the well-being of the individual participants.

As a matter of general beneficence, consideration should be given to enhancing benefits to participants and their community, especially when such benefits can be provided easily and will not compromise the scientific validity of the study. However, such enhancements of benefits are not to be considered in the assessment of the risk-benefit ratio—or even of the social value—of the research study itself.

Third, the risks and potential benefits of the clinical research interventions to individual participants should be compared. In general, the more likely and/or more severe the potential risks, the greater in likelihood and/or magnitude the prospective benefits must be; conversely, research entailing potential risks that are less likely and/or of lower severity can have more uncertain and/or circumscribed potential benefits. Importantly, this comparison of

risks and benefits should take into account the context in which the participants live and the risks they actually face. 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, riskier research may be justifiable.⁶¹ Similarly, the net risk-benefit ratio for a particular study may be favorable in communities in which the social value of the research is high, yet may be unfavorable in communities in which the potential value is lower.

When potential benefits to participants from the research are proportional to the risks they face, then the additional social value of the research, assured by the fulfillment of the value and validity requirements, implies that the cumulative benefits of the research outweigh its net risks.

The notions of "proportionality" and potential benefits "outweighing" risks are metaphorical.⁴ Yet the absence of a mathematical formula to determine when the balance of risks and potential benefits is proportionate does not connote that such judgments are inherently haphazard or subjective. Instead, assessments of risks and potential benefits to the same individuals can appeal to explicit standards, informed by existing data on the potential types of harms and benefits, their likelihood of occurring, and their long-term consequences.⁴ Evaluations of the quality of books are not quantifiable either, but neither are they merely matters of subjective taste; comparing the quality of Shakespeare or Dostoevsky with Danielle Steel entails judgments based on shared standards that can be justified to others. Similarly, people routinely make discursively justifiable intrapersonal comparisons of risks and benefits for themselves, and even for others, such as children, friends, and employees without the aid of mathematical formulae.⁶²

Finally, a more complex evaluation is necessary when clinical research presents no or few potential benefits to individual participants, such as in Phase I safety and pharmacokinetic studies, and even in some epidemiology research, or when the risks outweigh the potential benefits to individual participants. In this case, a more complex evaluation, what Charles Weijer calls a "risk-knowledge" calculus,⁵⁷ is necessary. This calculus assesses whether the societal benefits in terms of knowledge gained justify the "excess" risks to individual participants.⁶³ Determining when potential social benefits outweigh net risks to individual participants requires interpersonal comparisons that are conceptually and practically more difficult than intrapersonal comparisons.⁶² However, policy makers are often required to make these kinds of comparisons, for example, when considering whether pollution and its attendant harms to some people are worth the potential benefits of higher employment and tax revenues to others. There is no settled framework for how potential social benefits should be "balanced" against individual risks. Indeed, the appeal to a utilitarian approach of maximization, as in cost-benefit analysis, is quite controversial both morally and because many risks and benefits of research are not readily quantifiable on commensurable scales.⁶⁴⁻⁶⁶ Nevertheless, these comparisons are made,⁶⁷ and regulations mandate that investigators and research review committees make them with respect to clinical research.^{4,5} When research risks exceed the combination of potential medical benefits to individuals and the benefit of useful knowledge to society, clinical research is not justifiable.

Independent Review

Independent ethical review of all clinical research protocols is necessary for two reasons: (1) to minimize concerns regarding researchers' conflicts of interest and (2) to ensure public accountability.^{21,22} Investigators inherently have multiple, legitimate interests—interests to conduct high quality research, to complete the research expeditiously, to protect research participants, to obtain funding and advance their careers, and so forth.^{18,19} Even for well-intentioned investigators, these diverse interests can generate conflicts that may unwittingly distort or undermine their judgments regarding the design, conduct, and analysis of research, as well as adherence to ethical requirements.^{19,68–70} Wanting to complete a study quickly may lead to the use of questionable scientific methods or to the use of readily available participants rather than fairer participant selection criteria; enthusiasm for and commitment to the research project may lead to overemphasis of potential benefits and underemphasis of potential harms to participants. Independent review by individuals unaffiliated with the clinical research study helps to minimize the potential impact of such conflicts of interest.^{21,22,34,71} In this way, independent reviewers can assure potential research participants that the study they are considering is ethical—that is, it will generate socially valuable information, and the risk-benefit ratio is favorable.

Independent review of clinical research is also important for a second, less emphasized, reason: social accountability.²¹ Clinical research imposes risks on participants for the benefit of society. An independent review of a study's compliance with ethical requirements assures members of society that people who enroll in trials will be treated ethically. Based on this review, members of society can have confidence that they will not benefit from the exploitation of other humans.

Four benchmarks help in fulfilling this principle. First, procedures established by law and regulation should be followed. Research has not revealed the best mechanism to conduct independent review.⁷² Consequently, the actual review mechanisms are usually determined by laws and regulations that vary both internationally and locally. For instance, some countries and institutions separate scientific and ethical review, whereas others integrate scientific and ethical assessments into a single review. Similarly, some countries have ethics review committees composed only of laypersons, whereas others have committees dominated by medical scientists and physicians. Nevertheless, prevailing laws and regulations establish the standards that should be followed for independent review. They should be amended as better processes are identified.

Second, whatever the process, the review must be independent and competent. Members of the review committees must be free of any conflicts with the researchers or the research study. The reviewers should not be collaborators on the research or with the researchers, and should not have any financial interests in the outcomes of the study. Similarly, reviewers should be excluded from the review if they have other conflicting interests, such as responsibility for the financial interests of the institution in which the research is conducted, that might preclude them from evaluating the protocols according to ethical principles and without bias. Similarly, the reviewers should have sufficient expertise—or be able to access advice—in the scientific, clinical, and statistical areas necessary to assess the research protocol. Training in research ethics for the reviewers may be necessary.

Third, the review should be transparent. This is especially important in multinational research in which differences in culture, practices, and understandings may yield different judgments. One fundamental aspect of transparency is that the reasons for decisions of the independent review committee are explained. This allows observers to assess whether the reasons are appropriate and relevant considerations have been addressed.

Finally, given the increasing complexity of research, multiple independent reviews frequently occur.^{73–75} Multiple independent reviews may seem to be required by law or regulation for multisite studies or studies conducted by investigators from multiple institutions. Importantly, however, the ethical principle of independent review does not require multiple reviews.⁷⁶ The only requirement is that the reviewers competently and independently assess relevant scientific and ethical considerations. Indeed, multiple reviews may have no added value or may even be counterproductive, by taking time and requiring adjudication without added protections.⁷² Such situations are unethical—resources are expended that produce no value or even waste value.⁴⁰

If there is disagreement among such reviews, it is important to clarify its nature. Disagreement may reflect different ways of balancing various principles and benchmarks, or the appropriateness of different ways of fulfilling them. That is, disagreement might reflect *how* the ethical principles are met, rather than *whether* they are met.⁷⁷ 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.⁷⁸ Only rarely are there fundamental disagreements about whether ethical principles and benchmarks are fulfilled. Unfortunately, there is no widely accepted procedure for adjudicating such conflicts. In practice, the requirements specified by the sponsor's review board are often determinative. This contravenes the principle of collaborative partnership and the notion that the community that assumes the risks of the research should make the assessment about the research protocol.⁷⁹

Informed Consent

No requirement has received as much explication as informed consent. The purpose of informed consent is to show respect for the autonomy of individuals.^{4,6,15,25,34,80–85} To enroll individuals in clinical research without their authorization is to treat them merely as a means to purposes and ends they may not endorse or even know about, denying them the opportunity to choose what projects they will pursue and subjecting them to Kantian-type exploitation.^{23–25} By allowing individuals to decide if—and how—they contribute to research, informed consent respects persons and their autonomy.^{4,25}

Valid informed consent requires that the consenting person has the capacity to understand and make decisions, receives relevant information about the research study, understands that information, and consents voluntarily and without coercion.^{4,15,25,34,80–84} Each of these elements is necessary to ensure that individuals make rational and free determinations of whether the research trial is consonant with their interests.⁸⁶

Seven benchmarks are necessary to fulfill the principle of informed consent. First, recruitment procedures and incentives for participants should be consistent with *cultural, political and social practices of the potential participants*. 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 upon the local economic and social context.⁸⁷ Although concerns about undue inducement are frequently raised,^{4,5,84} high potential social value and a favorable risk-benefit ratio—implying minimal net risks to the participants—dispel these concerns.⁸⁸⁻⁹¹ Indeed, worry about undue inducement could reduce compensation and some other benefits for participants and host communities. Paradoxically, balancing fair compensation and undue inducement may result in less compensation for members of impoverished communities and raise the specter of exploitation.^{26,88}

Second, both written and verbal disclosure of information should be sensitive to participants' culture and context. Disclosures should use the language, culturally appropriate idioms, and analogies of the prospective participants at a level they can understand. This entails a need for collaborative partnership. After disclosure, investigators should feel confident that participants understand the information and are consenting without any pressure or major misconceptions. In some cases, a formal assessment of understanding, monitoring of the consent process, or independent assessment of participants' capacity to consent may be warranted.⁹²

Third, the disclosure of information relevant to the research study must be complete and accurate, but not overwhelming. Providing less than complete and accurate information raises concerns about potential deception of participants. However, complete information does not imply lengthy or exhaustive disclosure forms detailing every aspect of the research study, which may be overwhelming to the participants. Indeed, shorter, more focused forms, without repetition and boilerplate disclosures, may be more effective.⁹³ Disclosure forms must balance completeness with not being overwhelming.

Fourth, some research entails enrollment of individuals unable to consent because of their age, permanent mental incapacity, an acute loss of mental functions, or other reasons. In these cases, researchers must have a strategy for obtaining permission from legally authorized representatives of the potential participants.^{15,83,84,94-99}

In some cases, "spheres of consent" ranging from spouses to heads of households to school principals to village elders or community leaders may be required before researchers can invite individual participation.^{30,100,101} With a few exceptions, such as emergency research, it is unacceptable to supplant individual consent of competent adults by family or community consent.¹⁰² The family or community gives permission only to approach individuals. When family or community permission to approach individuals is reasonable, special care should be given to assure that the individual can still refuse participation—that is, that there is no coercion.

Sixth, researchers should utilize consent procedures that are acceptable within the local context, while ensuring that an independent observer could verify voluntary participation by the individuals. For instance, U.S. regulations require a written signature.⁵ In many cases, this is an acceptable and efficient way to document consent authorization. However, in some cases, because of limited literacy or cultural differences, such requirements may be inappropriate and unethical.⁷⁷ Alternative methods to express consent, such as handshakes, embracing, or sharing a meal, are known.⁷⁷ Appropriate alternative procedures for documenting informed consent might include tape recordings or witnessed written documentation of these methods of consent.

Finally, special attention must be given to ensure that individuals are aware of their right to, and are actually free to, refuse to participate or to withdraw from research. A key element of informed consent is the ability to refuse or withdraw participation without penalty.¹⁰³ Prorating offered compensation and other research-related benefits may help to obviate possible familial or community coercion or retribution.

Respect for Participants

The ethical conduct of clinical research does not end when informed consent is obtained.^{21,22,104} Researchers have ongoing obligations to treat individuals with respect from the time they are approached—even if they refuse enrollment—throughout their participation and even after their participation ends. Respecting potential and enrolled participants entails multiple activities. First, and arguably most important, this principle requires monitoring the health and well-being of participants, and intervening to prevent or treat harms that might result from the adverse reactions, untoward events, or changes in clinical status associated with the research.¹⁰⁴ In some cases, research studies need to include procedures to adjust drug doses and even withdraw study participants because of adverse events. Furthermore, specific stopping rules may be necessary if excessive adverse events or benefits are identified.

Second, pledges of confidentiality should be honored and procedures to protect confidentiality implemented. Such procedures include securing databases, locking file cabinets containing data, coding specimens and data forms, as well as interviewing participants in private spaces where they cannot be overheard. In addition, it is important to alert participants that despite researchers' best efforts, absolute confidentiality cannot be guaranteed.

Third, respect includes permitting participants to change their minds, to decide that the research does not comport with their interests or preferences, and to withdraw without penalty. Fourth, as new information about the impact of the intervention or about the participant's clinical condition is gained during the course of the research, respect requires providing this new information to the participants. Researchers should also develop explicit strategies to inform participants and host communities of the results of the research. Having participated in research and assumed risks, the participants and host communities have a right to know what was found and its implications for public health and health-care policies.

Finally, plans should be made regarding the care of participants when the trial is over. In some cases, this may simply involve referral to a primary care provider. In other cases, this may require researchers to find creative strategies for providing access to treatments benefiting the participants, even when these interventions are unlicensed.

Characteristics of the Principles

The eight general principles and the benchmarks delineate a systematic and comprehensive way of assessing the ethics of particular clinical research.^{21,22} They provide a coherent and organized way for researchers, ethics reviewers, participants, and others to

evaluate a research protocol and to determine whether it fulfills ethical standards. They should not be seen as adding ethical requirements, but rather distilling and coherently articulating the ethical norms underlying much of the prevailing guidance. These principles and benchmarks offer a more organized and systematic delineation of what many researchers, ethics reviewers, and others already do.

Importantly, these principles are not independent of all other ethical principles. They operate within and presume compliance with more general moral norms, such as honesty and promise keeping.²² Similarly, these principles focus on what is required to evaluate research studies, not on the enforcement or proper conduct of the research itself. Having ethical researchers is important for implementation of the framework but not a requirement for evaluating the research protocol. Determining *what* is ethical and what needs to be enforced must be done prior to and should not be confused with *how* to implement an ethical protocol or to enforce the requirements.^{21,22}

These eight principles are necessary. The presumption is that they must all be fulfilled for a research protocol to be ethical. There is no picking and choosing. However, in specific cases, such as emergency research, informed consent may be legitimately waived. These principles are justified by ethical values that are widely recognized and accepted, that reasonable people would want to be treated in accordance with—avoidance of exploitation, the just distribution of benefits and burdens, beneficence, respect for persons, and so forth.^{105,106} These requirements are precisely the types of considerations that would be invoked to justify clinical research if it were challenged. The benchmarks provide more practical considerations for discerning satisfaction of the general principles.

The principles are sufficient. Fulfilling these eight principles means the research is ethical. Failing on any one principle—except for waiving informed consent in specific cases, in which waiving consent must be justified—makes the research unethical. The proposed benchmarks, however, may not be sufficient, and may need revision with experience and time. They certainly provide a useful first estimation of the kind of specific elements that need to be fulfilled.

These eight principles are universal; they apply in all countries and contexts, regardless of sponsorship. The principles are general statements of value; they must be elaborated by traditions of interpretation and require practical interpretation and specification. The benchmarks offer a first level of specification, indicating how to fulfill these principles. However, the details of this specification will inherently be context and culture dependent. This does not make them relativistic or less universal. It simply recognizes that applying ethical principles in the world requires taking facts into account, and these facts depend upon the context.

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.¹⁰⁷

Importantly, that there are eight principles suggests that the ethics of research is complex. Adherence to a single ethical principle rarely provides a complete solution; most situations implicate multiple principles.^{48,62,64,105,107–110} Consequently, the various principles and benchmarks will sometimes conflict. What is fair participant selection could at times increase risk; what is required for informed consent may sometimes compromise scientific validity. Unfortunately, there is no simple algorithm for determining how to balance or weigh these principles when they conflict. Different researchers and communities will balance the principles in different ways, some emphasizing informed consent, others the importance of minimizing risks or enhancing social value. Ignoring or rejecting basic principles in designing or conducting a research study could render it 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. Disagreement on the balancing of the various benchmarks does not necessarily make one assessment ethical and the other unethical. Rather, it reflects different, but perhaps legitimate, ways of resolving competing ethical claims.¹⁰⁷ In fact, this framework can help narrow disagreements and elucidate the different underlying views. When conflicts between principles and benchmarks occur, or when different groups weigh the principles differently, the important point is to be clear about the reasons for the evaluation and the differences. Ultimately, a thoughtful process of balancing ethical considerations can be as important as any particular judgment in the effort to ensure that research is conducted ethically.

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