What Makes Clinical Research Ethical?

Ezekiel J. Emanuel, MD, PhD
David Wendler, PhD
Christine Grady, PhD

Many believe that informed consent makes clinical research ethical. However, informed consent is neither necessary nor sufficient for ethical clinical research. Drawing on the basic philosophies underlying major codes, declarations, and other documents relevant to research with human subjects, we propose 7 requirements that systematically elucidate a coherent framework for evaluating the ethics of clinical research studies: (1) value—enhancements of health or knowledge must be derived from the research; (2) scientific validity—the research must be methodologically rigorous; (3) fair subject selection—scientific objectives, not vulnerability or privilege, and the potential for and distribution of risks and benefits, should determine communities selected as study sites and the inclusion criteria for individual subjects; (4) favorable risk-benefit ratio—within the context of standard clinical practice and the research protocol, risks must be minimized, potential benefits enhanced, and the potential benefits to individuals and knowledge gained for society must outweigh the risks; (5) independent review—unaffiliated individuals must review the research and approve, amend, or terminate it; (6) informed consent—individuals should be informed about the research and provide their voluntary consent; and (7) respect for enrolled subjects—subjects should have their privacy protected, the opportunity to withdraw, and their well-being monitored. Fulfilling all 7 requirements is necessary and sufficient to make clinical research ethical. These requirements are universal, although they must be adapted to the health, economic, cultural, and technological conditions in which clinical research is conducted.

JAMA. 2000;283:2701-2711 www.jama.com

WHAT MAKES RESEARCH involving human subjects ethical? Informed consent is the answer most US researchers, bioethicists, and institutional review board (IRB) members would probably offer. This response reflects the preponderance of existing guidance on the ethical conduct of research and the near obsession with autonomy in US bioethics.[1-4] While informed consent is necessary in most but not all cases, in no case is it sufficient for ethical clinical research.[5-8] Indeed, some of the most contentious contemporary ethical controversies in clinical research, such as clinical research in developing countries,[9-13] the use of placebos,[14-16] phase 1 research,[17-19] protection for communities,[20-24] and involvement of children,[25-29] raise questions not of informed consent, but of the ethics of subject selection, appropriate risk-benefit ratios, and the value of research to society. Since obtaining informed consent does not ensure ethical research, it is imperative to have a systematic and coherent framework for evaluating clinical studies that incorporates all relevant ethical considerations.

In this article, we delineate 7 requirements that provide such a framework by synthesizing traditional codes, declarations, and relevant literature on the ethics of research with human subjects. This framework should help guide the ethical development and evaluation of clinical studies by investigators, IRB members, funders, and others.

THE 7 ETHICAL REQUIREMENTS

The overarching objective of clinical research is to develop generalizable knowledge to improve health and/or increase understanding of human biology[30,31]; subjects who participate are the means to securing such knowledge.[32] By placing some people at risk of harm for the good of others, clinical research has the potential for exploitation of human subjects.[33,34] Ethical requirements for clinical research aim to minimize the possibility of exploitation by ensuring that research subjects are not merely used but are treated with respect while they contribute to the social good.[30]

For the past 50 years, the main sources of guidance on the ethical conduct of clinical research have been the Nuremberg Code,[35] Declaration of Helsinki,[36] Belmont Report,[37] International Ethical Guidelines for Biomedical Research Involving Human Subjects,[38] and similar documents (TABLE 1). However, many of these documents were written in response to specific events and to avoid future scandals.[50,51] By focusing on the instigating issues, these guidelines tend to

Author Affiliations: Department of Clinical Bioethics, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, Md.
Corresponding Author and Reprints: Christine Grady, PhD, Warren G. Magnuson Clinical Center, Bldg 10, Room 1C118, National Institutes of Health, Bethesda, MD 20892-1156 (e-mail: cgrady@nih.gov).

emphasize certain ethical requirements while eliding others. For instance, the Nuremberg Code[35] was part of the judicial decision condemning the atrocities of the Nazi physicians and so focused on the need for consent and a favorable risk-benefit ratio but makes no mention of fair subject selection or independent review. The Declaration of Helsinki[36] was developed to remedy perceived lacunae in the Nuremberg Code, especially as related to physicians conducting research with patients, and so focuses on favorable risk-benefit ratio and independent review; the Declaration of Helsinki also emphasizes a distinction between therapeutic and nontherapeutic research that is rejected or not noted by other documents.[30,52] The Belmont Report[37] was meant to provide broad principles that could be used to generate specific rules and regulations in response to US research scandals such as Tuskegee[53] and Willowbrook.[54,55] It focuses on informed consent, favorable risk-benefit ratio, and the need to ensure that vulnerable populations are not targeted for risky research. The Council for International Organizations of Medical Sciences (CIOMS) guidelines[38] were intended to apply the Declaration of Helsinki "in developing countries . . . [particularly for] large-scale trials of vaccines and drugs." The CIOMS guidelines lack a separate section devoted to risk-benefit ratios, although the council considers this issue in commentary on other guidelines. It also includes a section on compensation for research injuries not found in other documents. Because the Advisory Committee on Human Radiation Experiments was responding to covert radiation experiments, avoiding deception was among its 6 ethical standards and rules; most other major documents do not highlight this.[56] This advisory committee claims that its ethical standards are general, but acknowledges that its choices were related to the specific circumstances that occasioned the report.[56] Finally some tensions, if not outright contradictions, exist among the provisions of the various guidelines.[5,19,30,51,52,57,58] Absent a universally applicable ethical framework, investigators, IRB members, funders, and others lack coherent guidance on determining whether specific clinical research protocols are ethical.

Table 1. Selected Guidelines on the Ethics of Biomedical Research With Human Subjects*

Guideline	Source	Year and Revisions
	Fundamental	
Nuremberg Code[35]	Nuremberg Military Tribunal decision in *United States v Brandt*	1947
Declaration of Helsinki[36]	World Medical Association	1964, 1975, 1983, 1989, 1996
Belmont Report[37]	National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research	1979
International Ethical Guidelines for Biomedical Research Involving Human Subjects[38]	Council for International Organizations of Medical Sciences in collaboration with World Health Organization	Proposed in 1982; revised, 1993
	Other	
45 CFR 46, Common Rule[8]	US Department of Health and Human Services (DHHS) and other US federal agencies	DHHS guidelines in 1981; Common Rule, 1991
Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products[42]	World Health Organization	1995
Good Clinical Practice: Consolidated Guidance[44]	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use	1996
Convention on Human Rights and Biomedicine[43]	Council of Europe	1997
Guidelines and Recommendations for European Ethics Committees[45]	European Forum for Good Clinical Practice	1997
Medical Research Council Guidelines for Good Clinical Practice in Clinical Trials[46]	Medical Research Council, United Kingdom	1998
Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda[47]	Uganda National Council for Science and Technology	1998
Ethical Conduct for Research Involving Humans[48]	Tri-Council Working Group, Canada	1998
National Statement on Ethical Conduct in Research Involving Humans[49]	National Health and Medical Research Council, Australia	1999

*CFR indicates Code of Federal Regulations. More extensive lists of international guidelines on human subjects research can be found in Brody[39] and Fluss.[40] An extensive summary of US guidelines can be found in Sugarman et al.[41]

There are 7 requirements that provide a systematic and coherent framework for determining whether clinical research is ethical (TABLE 2). These requirements are listed in chronological order from the conception of the research to its formulation and implementation. They are meant to guide the ethical development, implementation, and review of individual clinical protocols. These 7 requirements are intended to elucidate the ethical standards specific for clinical research and assume general ethical obligations, such as intellectual honesty and responsibility. While none of the traditional ethical guidelines on clinical research explicitly includes all 7 requirements, these requirements systematically elucidate the fundamental protections embedded in the basic philosophy of all these documents.[30] These requirements are not limited to a specific tragedy or scandal or to the practices of researchers in 1 country; they are meant to be universal, although their application will require adaptation to particular cultures, health conditions, and economic settings. These

7 requirements can be implemented well or ineffectively. However, their systematic delineation is important and conceptually prior to the operation of an enforcement mechanism. We need to know what to enforce.

Value

To be ethical, clinical research must be valuable,[4,35] meaning that it evaluates a diagnostic or therapeutic intervention that could lead to improvements in health or well-being; is a preliminary etiological, pathophysiological, or epidemiological study to develop such an intervention; or tests a hypothesis that can generate important knowledge about structure or function of human biological systems, even if that knowledge does not have immediate practical ramifications.[4,30] Examples of research that would not be socially or scientifically valuable include clinical research with nongeneralizable results, a trifling hypothesis, or substantial or total overlap with proven results.[4] In addition, research with results unlikely to be disseminated or in which the intervention could never be practically implemented even if effective is not valuable.[12,13,38,59] Only if society will gain knowledge, which requires sharing results, whether positive or negative, can exposing human subjects to risk in clinical research be justified. Thus, evaluation of clinical research should ensure that the results will be disseminated, although publication in peer-reviewed journals need not be the primary or only mechanism.

There are 2 fundamental reasons why social, scientific, or clinical value should be an ethical requirement: responsible use of finite resources and avoidance of exploitation.[4] Research resources are limited. Even if major funding agencies could fund all applications for clinical research, doing so would divert resources from other worthy social pursuits. Beyond not wasting resources, researchers should not expose human beings to potential harms without some possible social or scientific benefit.[4,30,35,38]

It is possible to compare the relative value of different clinical research studies; clinical research that is likely to generate greater improvements in health or well-being given the condition being investigated, the state of scientific understanding, and the feasibility of implementing the intervention is of higher value. Comparing relative value is integral to determinations of funding priorities when allocating limited funds among alternative research proposals.[60] Similarly, a comparative evalu-

Table 2. Seven Requirements for Determining Whether a Research Trial Is Ethical*

Requirement	Explanation	Justifying Ethical Values	Expertise for Evaluation
Social or scientific value	Evaluation of a treatment, intervention, or theory that will improve health and well-being or increase knowledge	Scarce resources and nonexploitation	Scientific knowledge; citizen's understanding of social priorities
Scientific validity	Use of accepted scientific principles and methods, including statistical techniques, to produce reliable and valid data	Scarce resources and nonexploitation	Scientific and statistical knowledge; knowledge of condition and population to assess feasibility
Fair subject selection	Selection of subjects so that stigmatized and vulnerable individuals are not targeted for risky research and the rich and socially powerful not favored for potentially beneficial research	Justice	Scientific knowledge; ethical and legal knowledge
Favorable risk-benefit ratio	Minimization of risks; enhancement of potential benefits; risks to the subject are proportionate to the benefits to the subject and society	Nonmaleficence, beneficence, and nonexploitation	Scientific knowledge; citizen's understanding of social values
Independent review	Review of the design of the research trial, its proposed subject population, and risk-benefit ratio by individuals unaffiliated with the research	Public accountability; minimizing influence of potential conflicts of interest	Intellectual, financial, and otherwise independent researchers; scientific and ethical knowledge
Informed consent	Provision of information to subjects about purpose of the research, its procedures, potential risks, benefits, and alternatives, so that the individual understands this information and can make a voluntary decision whether to enroll and continue to participate	Respect for subject autonomy	Scientific knowledge; ethical and legal knowledge
Respect for potential and enrolled subjects	Respect for subjects by (1) permitting withdrawal from the research; (2) protecting privacy through confidentiality; (3) informing subjects of newly discovered risks or benefits; (4) informing subjects of results of clinical research; (5) maintaining welfare of subjects	Respect for subject autonomy and welfare	Scientific knowledge; ethical and legal knowledge; knowledge of particular subject population

*Ethical requirements are listed in chronological order from conception of research to its formulation and implementation.

ation of value may be necessary in considering studies involving finite scientific resources such as limited biological material or the small pool of long-term human immunodeficiency virus nonprogressors.

Scientific Validity

To be ethical, valuable research must be conducted in a methodologically rigorous manner.[4] Even research asking socially valuable questions can be designed or conducted poorly and produce scientifically unreliable or invalid results.[61] As the CIOMS guidelines succinctly state: "Scientifically unsound research on human subjects is ipso facto unethical in that it may expose subjects to risks or inconvenience to no purpose."[38]

For a clinical research protocol to be ethical, the methods must be valid and practically feasible: the research must have a clear scientific objective; be designed using accepted principles, methods, and reliable practices; have sufficient power to definitively test the objective; and offer a plausible data analysis plan.[4] In addition, it must be possible to execute the proposed study. Research that uses biased samples, questions, or statistical evaluations, that is underpowered, that neglects critical end points, or that could not possibly enroll sufficient subjects cannot generate valid scientific knowledge and is thus unethical.[4,30,62] For example, research with too few subjects is not valid because it might be combined in a meaningful meta-analysis with other, as yet unplanned and unperformed clinical research; the ethics of a clinical research study cannot depend on the research that others might but have not yet done. Of course the development and approval of a valid method is of little use if the research is conducted in a sloppy or inaccurate manner; careless research that produces uninterpretable data is not just a waste of time and resources, it is unethical.

Clinical research that compares therapies must have "an honest null hypothesis" or what Freedman called clinical equipoise.[30,63] That is, there must be controversy within the scientific community about whether the new intervention is better than standard therapy, including placebo, either because most clinicians and researchers are uncertain about whether the new treatment is better, or because some believe the standard therapy is better while others believe the investigational intervention superior.[63] If there exists a consensus about what is the better treatment, there is no null hypothesis, and the research is invalid. In addition, without clinical equipoise, research that compares therapies is unlikely to be of value because the research will not contribute to increasing knowledge about the best therapy, and the risk-benefit ratio is unlikely to be favorable because some of the subjects will receive inferior treatment.

Importantly, a "good question" can be approached by good or bad research techniques; bad research methods do not render the question valueless. Thus, the significance of a hypothesis can and should be assessed prior to and independent of the specific research methods. Reviewers should not dismiss a proposal that uses inadequate methods without first considering whether adjustments could make the proposal scientifically valid.

The justification of validity as an ethical requirement relies on the same 2 principles that apply to value—limited resources and the avoidance of exploitation.[4,30] "Invalid research is unethical because it is a waste of resources as well: of the investigator, the funding agency, and anyone who attends to the research."[4] Without validity the research cannot generate the intended knowledge, cannot produce any benefit, and cannot justify exposing subjects to burdens or risks.[50]

Fair Subject Selection

The selection of subjects must be fair.[30,37,56] Subject selection encompasses decisions about who will be included both through the development of specific inclusion and exclusion criteria and the strategy adopted for recruiting subjects, such as which communities will be study sites and which potential groups will be approached. There are several facets to this requirement.

First, fair subject selection requires that the scientific goals of the study, not vulnerability, privilege, or other factors unrelated to the purposes of the research, be the primary basis for determining the groups and individuals that will be recruited and enrolled.[3,30,37] In the past, groups sometimes were enrolled, especially for research that entailed risks or offered no potential benefits, because they were "convenient" or compromised in their ability to protect themselves, even though people from less vulnerable groups could have met the scientific requirements of the study.[30,37,53,54]

Similarly, groups or individuals should not be excluded from the opportunity to participate in research without a good scientific reason or susceptibility to risk that justifies their exclusion.[64] It is important that the results of research be generalizable to the populations that will use the intervention. Efficiency cannot override fairness in recruiting subjects.[37] Fairness requires that women be included in the research, unless there is good reason, such as excessive risks, to exclude them.[65-69] This does not mean that every woman must be offered the opportunity to participate in research, but it does mean that women as a class cannot be peremptorily excluded.

Second, it is important to recognize that subject selection can affect the risks and benefits of the study.[70] Consistent with the scientific goals, subjects should be selected to minimize risks and enhance benefits to individual subjects and society. Subjects who are eligible based on the scientific objectives of a study, but are at substantially higher risk of being harmed or experiencing more severe harm, should be excluded from participation.[71] Selecting subjects to enhance benefits entails consideration of which subjects will maximize the benefit or value of the information obtained. If a potential drug or procedure is likely to be prescribed for women or children if proven safe and effective, then these groups should be

included in the study to learn how the drug affects them.[63,66,67] Indeed, part of the rationale for recent initiatives to include more women, minorities, and children in clinical research is to maximize the benefits and value of the study by ensuring that these groups are enrolled.[65-67,72,73] It is not necessary to include children in all phases of research. Instead, it may be appropriate to include them only after the safety of the drug has been assessed in adults.

Additionally, fair subject selection requires that, as far as possible, groups and individuals who bear the risks and burdens of research should be in a position to enjoy its benefits,[12,13,38,59,74] and those who may benefit should share some of the risks and burdens.[75] Groups recruited to participate in clinical research that involves a condition to which they are susceptible or from which they suffer are usually in a position to benefit if the research provides a positive result, such as a new treatment. For instance, selection of subjects for a study to test the efficacy of an antimalarial vaccine should consider not only who will best answer the scientific question, but also whether the selected groups will receive the benefits of the vaccine, if proven effective.[12,13,37,59,74,76] Groups of subjects who will predictably be excluded as beneficiaries of research results that are relevant to them typically should not assume the burdens so that others can benefit. However, this does not preclude the inclusion of subjects who are scientifically important for a study but for whom the potential products of the research may not be relevant, such as healthy control subjects.

Fair subject selection should be guided by the scientific aims of the research and is justified by the principles that equals should be treated similarly and that both the benefits and burdens generated by social cooperation and activities such as clinical research should be distributed fairly.[3,30,37,38,66,67] This does not mean that individual subjects and members of groups from which they are selected must directly benefit from each clinical research project or that people who are marginalized, stigmatized, powerless, or poor should never be included. Instead, the essence of fairness in human subjects research is that scientific goals, considered in dynamic interaction with the potential for and distribution of risks and benefits, should guide the selection of subjects.

Favorable Risk-Benefit Ratio

Clinical research involves drugs, devices, and procedures about which there is limited knowledge. As a result, research inherently entails uncertainty about the degree of risk and benefits, with earlier phase research having greater uncertainty. Clinical research can be justified only if, consistent with the scientific aims of the study and the relevant standards of clinical practice, 3 conditions are fulfilled: the potential risks to individual subjects are minimized, the potential benefits to individual subjects are enhanced, and the potential benefits to individual subjects and society are proportionate to or outweigh the risks.[30,36,37]

Assessment of the potential risks and benefits of clinical research by researchers and review bodies typically involves multiple steps. First, risks are identified and, within the context of good clinical practice, 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."[8]

Second, potential benefits to individual subjects from the research are delineated and enhanced. Potential benefits focus on the benefits to individual subjects, such as health improvements, because the benefits to society through the generation of knowledge are assumed if the research is deemed to be of value and valid. The specification and enhancement of potential benefits to individual subjects should consider only health-related potential benefits derived from the research.[77] Assessment of the research plan should determine if changes could enhance the potential benefits for individual subjects. For example, consistent with the scientific objectives, tests and interventions should be arranged to increase benefit to subjects. However, extraneous benefits, such as payment, or adjunctive medical services, such as the possibility of receiving a hepatitis vaccine not related to the research, cannot be considered in delineating the benefits compared with the risks, otherwise simply increasing payment or adding more unrelated services could make the benefits outweigh even the riskiest research. Furthermore, while participants in clinical research may 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 subjects.

In the final step, risks and potential benefits of the clinical research interventions to individual subjects are compared. In general, the more likely and/or 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. If the potential benefits to subjects are proportional to the risks they face, as generally found when evaluating phase 2 and 3 research, then the additional social benefits of the research, assured by the fulfillment of the value and validity requirements, imply that the cumulative benefits of the research outweigh its risks.[30]

Obviously, the notions of "proportionality" and potential benefits "outweighing" risks are nonquantifiable.[37] However, the absence of a 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.[37] 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.[78]

An additional evaluation is necessary for any clinical research that presents no potential benefits to individual subjects, such as phase 1 safety, pharmacokinetic, and even some epidemiology research, or when the risks outweigh the potential benefits to individual subjects.[72] This determination, which Weijer[79] calls a "risk-knowledge calculus," assesses whether the societal benefits in terms of knowledge justify the excess risks to individual subjects. Determination of when potential social benefits outweigh risks to individual subjects requires interpersonal comparisons that are conceptually and practically more difficult.[78] However, policymakers often are required to make these kind 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.[78-82] Nevertheless, these comparisons are made,[83] and regulations mandate that investigators and IRBs make them with respect to clinical research. When research risks exceed potential medical benefits to individuals and the benefit of useful knowledge to society, the clinical research is not justifiable.

The requirement for a favorable risk-benefit ratio embodies the principles of nonmaleficence and beneficence, long recognized as fundamental values of clinical research.[3,30,36,37] The principle of nonmaleficence states that one ought not to inflict harm on a person.[3] This justifies the need to reasonably reduce the risks associated with research. The principle of beneficence "refers to a moral obligation to act for the benefit of others."[3] In clinical research, this translates into the need to enhance the potential benefits of the research for both individual subjects and society.[3,30,37] Ensuring that the benefits outweigh the risks is required by the need to avoid the exploitation of subjects.[30,37]

Independent Review

Investigators inherently have multiple, legitimate interests—interests to conduct high-quality research, complete the research expeditiously, protect research subjects, obtain funding, and advance their careers. These diverse interests can generate conflicts that may unwittingly distort the judgment of even well-intentioned investigators regarding the design, conduct, and analysis of research.[84-87] Wanting to complete a study quickly may lead to the use of questionable scientific methods or readily available rather than the most appropriate subjects. Independent review by individuals unaffiliated with the clinical research helps minimize the potential impact of such conflicts of interest.[86,88] For some research with few or no risks, independent review may be expedited, but for much of clinical research, review should be done by a full committee of individuals with a range of expertise who have the authority to approve, amend, or terminate a study.

Independent review of clinical research is also important for social accountability. Clinical research imposes risks on subjects for the benefit of society. Independent review of a study's compliance with ethical requirements assures members of society that people who enroll in trials will be treated ethically and that some segments of society will not benefit from the misuse of other human beings. Review also assures people that if they enroll in clinical research, the trial is ethically designed and the risk-benefit ratio is favorable.

In the United States, independent evaluation of research projects occurs through multiple groups including granting agencies, local IRBs, and data and safety monitoring boards.[89-91] In other countries, independent review of clinical research is conducted in other ways.

Informed Consent

Of all requirements, none has received as much explication as informed consent.[2-4,6,7,19,30-32,35-38] The purpose of informed consent is 2-fold: to ensure that individuals control whether or not they enroll in clinical research and participate only when the research is consistent with their values, interests, and preferences.[2,3,30-32,35,37,92-96] To provide informed consent, individuals must be accurately informed of the purpose, methods, risks, benefits, and alternatives to the research; understand this information and its bearing on their own clinical situation; and make a voluntary and uncoerced decision whether to participate.[97-99] 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.

Informed consent embodies the need to respect persons and their autonomous decisions.[2,3,97,98] 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 and deny them the opportunity to choose what projects they will pursue.

Children and adults with diminished mental capacity who are unable to make their own decisions about participating in research nonetheless have interests and values.[2,3] For instance, individuals rendered unconscious due to head trauma or a stroke typically retain the interests and values they had just before the accident. Even individuals with severe Alzheimer disease retain some interests, if only those related to personal dignity and physical comfort. Showing respect for these nonautonomous persons means ensuring that research participation is consistent with their interests and values; this

usually entails empowering a proxy decision maker to determine whether to enroll the person in clinical research. In making this decision, the proxy uses the substituted judgment standard: what research decision would the subject make if he or she could.[2,3,100]

However, an individual's preferences and values related to clinical research may be unknown or unknowable, or, in the case of children, the individual may not have developed mature preferences related to research. In such cases, research proxies should choose the option that is in the individual's best medical interests. There is controversy about how much discretion proxies should have in such circumstances, especially given the inherent uncertainty of the risks and potential benefits of research participation.[101-105] The National Bioethics Advisory Commission has urged that proxies should exercise "great caution" in making judgments about a subject's best interest regarding research.[103] Other groups believe that proxies should have more discretion.

In emergency settings that preclude time for identifying and eliciting the consent of a proxy decision maker, research can proceed without either informed consent or permission of proxy decision makers when conducted under strict guidelines.[6] Most importantly, there should be clinical equipoise—the absence of a consensus regarding the comparative merits of the interventions to be tested.[63] In such a case, the subject is not worse off by enrolling.

Respect for Potential and Enrolled Subjects

Ethical requirements for clinical research do not end when individuals either sign the consent form and are enrolled or refuse enrollment.[106] Individuals must continue to be treated 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 subjects entails at least 5 different activities. First, since substantial information will be collected about potential as well as enrolled subjects, their privacy must be respected by managing the information in accordance with confidentiality rules. Second, respect includes permitting subjects to change their mind, to decide that the research does not match their interests, and to withdraw without penalty. Third, in the course of clinical research new information about the effect of the intervention or the subject's clinical condition may be gained. Respect requires that enrolled subjects be provided with this new information. For instance, when informed consent documents are modified to include additional risks or benefits discovered in the course of research, subjects already enrolled should be informed. Fourth, the welfare of subjects should be carefully monitored throughout their research participation. If subjects experience adverse reactions, untoward events, or changes in clinical status, they should be provided with appropriate treatment and, when necessary, removed from the study. Finally, to recognize subjects' contribution to clinical research, there should be some mechanism to inform them of what was learned from the research.

For commentators used to thinking about respect in terms of privacy and confidentiality alone, these different activities may seem a haphazard agglomeration of informed consent, confidentiality, and other protections. In fact, this requirement integrates into a coherent framework actions the commonality of which often goes unrecognized. As such, it reminds investigators, subjects, IRB members, and others that respect for subjects requires the respectful treatment of individuals who choose not to enroll and the careful ongoing monitoring of those who do, in addition to ensuring the privacy and confidentiality of enrolled subjects. This requirement emphasizes that the ethics of clinical research do not end with the signing of a consent document but encompass the actual implementation, analysis, and dissemination of research. Indeed, it suggests that although "human subjects" is the prevailing designation, the term *subject* may not fully reflect appropriate respect: human research participant or partner may be more appropriate terminology.

Respect for potential and enrolled subjects is justified by multiple principles including beneficence, nonmaleficence, and respect for persons.[3] Permitting subjects to withdraw and providing them additional information learned from the research are key aspects of respecting subject autonomy.[3,37] Protecting confidentiality and monitoring well-being are motivated by respect for persons, beneficence, and nonmaleficence.[3]

ARE THESE ETHICAL REQUIREMENTS NECESSARY AND SUFFICIENT?

Value, validity, fair subject selection, favorable risk-benefit ratio, and respect for subjects embody substantive ethical values. As such, they are all necessary: clinical research that neglected or violated any of these requirements would be unethical. Conversely, independent review and informed consent are procedural requirements intended to minimize the possibility of conflict of interest, maximize the coincidence of the research with subjects' interests, and respect their autonomy.[30] However, other procedures may also achieve these results. For instance, evidence of an individual's preferences regarding research may be obtained from a research advance directive rather than the individual's concurrent informed consent.[103] Given the existence of alternative procedures, informed consent requirements can be minimized, and, in some circumstances, consent can even be waived.[7,101,103] Research on emergency life-saving interventions for subjects who are unconscious or otherwise not mentally capable of consent and for whom family or proxy consent is not immediately available may be conducted without informed consent.[6,107-109] Thus, all requirements need to be satisfied, but they may have to be adjusted and balanced given the circumstances of different types of research.

As interpreted and elaborated for specific research protocols, the fulfillment of each of these 7 requirements ensures that research is socially valuable and subjects are not exploited, that subjects are treated fairly and with respect, and that their interests are protected. As a result, these requirements should be sufficient to ensure that the vast majority of clinical research is ethical.[30] While it may be impossible to exclude the possibility that additional requirements are needed in rare cases, these 7 requirements are the essential ones.

UNIVERSALITY OF THE REQUIREMENTS

These 7 requirements for ethical clinical research are also universal.[35-49,110] They are justified by ethical values that are widely recognized and accepted and in accordance with how reasonable people would want to be treated.[110-112] Indeed, these requirements are precisely the types of considerations that would be invoked to justify clinical research if it were challenged.

Like constitutional provisions and amendments, these ethical requirements are general statements of value that must be elaborated by traditions of interpretation and that require practical interpretation and specification that will inherently be context and culture dependent.[110-113] For instance, while informed consent is meant to ensure that research subjects are treated with respect, what constitutes respect varies from culture to culture.[110,114] In some places, it will be necessary to elicit the consent of elders before individual subjects can be approached for informed consent.[115] Similarly, who is considered vulnerable for the purposes of fair subject selection criteria will vary by locale. While in the United States special efforts are necessary to ensure that racial minorities are not just targeted for research with high potential for risks,[53,73] in other places fair subject selection may require special focus on religious groups. Similarly, local traditions and economic conditions will influence when financial payments may constitute undue inducements. Also, whether research has a favorable risk-benefit ratio will depend on the underlying health risks in a society. Research that is unacceptable in one society because its risks outweigh the risks posed by the disease may have a favorable risk-benefit ratio in another society where the risks posed by the disease are significantly greater. Adapting these requirements to the identities, attachments, and cultural traditions embedded in distinct circumstances neither constitutes moral relativism nor undermines their universality[110-112]; doing so recognizes that while ethical requirements embody universal values, the manner of specifying these values inherently depends on the particular context.[110-112]

NECESSARY EXPERTISE

These ethical requirements emphasize the type of training and skills necessary for clinical investigators and those conducting independent review (Table 2). Not only must clinical investigators be skilled in the appropriate methods, statistical tests, outcome measures, and other scientific aspects of clinical trials, they must have the training to appreciate, affirm, and implement these ethical requirements, such as the capacity and sensitivity to determine appropriate subject selection criteria, evaluate risk-benefit ratios, provide information in an appropriate manner, and implement confidentiality procedures. Similarly, because independent review of clinical research must assess its value, validity, selection criteria, risk-benefit ratios, informed consent process, and procedures for monitoring enrolled subjects, the necessary skills must range from scientific to ethical to lay knowledge. Consequently, the independent ethical review of research trials should involve individuals with training in science, statistics, ethics, and law, as well as reflective citizens who understand social values, priorities, and the vulnerability and concerns of potential subjects (Table 2).

ACTUAL CASES

Considering actual cases illuminates how the requirements can guide ethical evaluation of clinical research. One persistently controversial issue is the use of placebo controls.[14-16] A new class of antiemetics, serotonin antagonists, such as ondansetron hydrochloride and granistron hydrochloride, were developed about 10 years ago. To evaluate these drugs, investigators conducted placebo-controlled trials randomizing cancer patients receiving emetogenic chemotherapy to either placebo or the serotonin antagonists.[116-118]

In evaluating the ethics of this clinical research, all requirements need to be fulfilled, but 3 requirements seem particularly relevant: value, scientific validity, and risk-benefit ratio. There is no doubt that the dominant antiemetic therapies of the time, such as prochlorperazine, metoclopramide hydrochloride, and high-dose corticosteroids are effective. However, they are not completely effective, especially for strongly emetogenic chemotherapy such as platinum, and they have significant adverse effects, especially dystonic reactions. Alternative antiemetic therapies that would be more effective and have fewer adverse effects were viewed as desirable and of value. However, there was no value in knowing whether the serotonin antagonists were better than placebo in controlling emesis, since placebo was not the standard of care at the time of the research.[14,63] Even if the serotonin antagonists were shown to be more effective than placebo, it would be a further issue to evaluate their effectiveness and adverse-event profile compared with the extant interventions. Thus, a placebo-controlled trial of the serotonin antagonists for chemotherapy-induced emesis does not fulfill the value requirement.

Comparative studies evaluating the difference between 2 active treatments are common in cancer therapy and valid as a study design.[14-16] Some argue that active-controlled studies are scientifically more difficult to conduct than placebo-controlled trials.[119] However, any ethically and scientifically valid randomized trial requires that there be an honest null hypothesis.[30,63] The null hypothesis that the serotonin antagonists are equivalent to

placebo was not reasonable at the time of the clinical research.[14,63] Indeed, coeval with the placebo-controlled studies were randomized controlled trials with serotonin antagonists vs active antiemetic therapy.[120,121] Thus, a placebo-controlled trial was not the only scientifically valid method.

Those who supported the notion of a randomized, placebo-controlled trial of serotonin antagonists argued that there was no serious risk from using a placebo because emesis is a transitory discomfort that results in no permanent disability.[119,122] However, emesis is not pleasant. Indeed, the entire rationale for developing serotonin antagonists is that chemotherapy-induced emesis is a sufficiently serious health problem that development and use of effective interventions in clinical practice are justifiable and desirable.[123] As one published report of a randomized placebo-controlled trial of ondansetron stated to justify the research: "Uncontrolled nausea and vomiting [from chemotherapy] frequently results in poor nutritional intake, metabolic derangements, deterioration of physical and mental condition, as well as the possible rejection of potentially beneficial treatment. Many patients are more afraid of uncontrolled nausea and vomiting than of alopecia."[118]

Furthermore, the placebo-controlled trials for antiemetics included "'rescue' medication if patients had persistent nausea or vomiting."[118] This indicates both that there was an alternative standard treatment for chemotherapy-induced emesis and that emesis was sufficiently harmful to require intervention.[14,15,123,124] Permitting patients to vomit while being administered placebo causes them unnecessary harm.[14,123,124] Thus, a placebo-controlled trial of antiemetics for chemotherapy-induced emesis does not minimize harm in the context of good clinical practices and so fails the favorable risk-benefit ratio when an available clinical intervention can partially ameliorate some of the harm.[123]

Importantly, the evaluation of these placebo-controlled trials of antiemetics did not need to address informed consent to determine whether they were ethical.[122] Indeed, even if patients had signed an informed consent document that indicated they could be randomized to placebo and that there were alternative effective treatments, the placebo-controlled research on serotonin antagonists would still be unethical.

Another controversial issue involves research in developing countries.[9-13,57,59] Recently, a rhesus rotavirus tetravalent (RRV-TV) vaccine was licensed in the United States after randomized trials in developed countries demonstrated a 49% to 68% efficacy in preventing diarrhea and up to 90% efficacy in preventing severe cases of diarrhea.[125-127] However, shortly after approval, the vaccine was withdrawn from the US market because of a cluster of cases of intussusception, representing an approximately 1 in 10 000 added risk of this complication.[128] Should randomized controlled trials of RRV-TV vaccine proceed as planned in developing countries or wait for a new vaccine candidate to be developed? (C. Weijer, MD, PhD, written communication, March 24, 2000) In evaluating the ethics of these proposed trials, the requirements of value, scientific validity, fair subject selection, and risk-benefit ratio are particularly relevant.

Despite oral rehydration therapy, more than 600 000 children in developing countries die annually from rotavirus diarrhea.[129] In some countries, the death rate from rotavirus is nearly 1 in 200. Clearly, a rotavirus vaccine with even 80% efficacy that prevented more than half a million deaths would be of great value. But is research using the RRV-TV vaccine ethical when the risk of intussusception stopped its use in the United States? The RRV-TV vaccine was the first and only licensed rotavirus vaccine and has already been administered to nearly 1 million children; potential alternative rotavirus vaccines are still years away from phase 3 research. Thus, given the potential benefit of preventing deaths from rotavirus in developing countries, a trial of RRV-TV vaccine now—even if a better vaccine becomes evaluable in a few years—is worthwhile. There is value to the research on the vaccine for developing countries only if there is reasonable assurance children in the country would be able to obtain it if it proved effective.[12,13,59]

Vaccines effective in developed countries may or may not be as effective or safe in developing countries. Host, viral, and environmental factors and seasonality of the disease can alter the efficacy and safety profiles of a vaccine.[130] Thus, there is good scientific rationale for determining whether the RRV-TV vaccine can achieve sufficient levels of protection against diarrhea with an acceptably low incidence of complications in children in developing countries. In this case, given the lack of an established method of preventing rotavirus infections in these countries, a placebo-controlled trial would be valid.

Two factors suggest that, in the RRV-TV vaccine study, subjects in developing countries are being selected for reasons of science and not being exploited. First, the most appropriate subjects for a rotavirus vaccine trial are infants and children who have a high incidence of rotavirus infection and who experience significant morbidity and mortality from the infection. In such a population the efficacy of the vaccine would be most apparent. Second, since the RRV-TV vaccine has been withdrawn from the US market, children in developing countries are not being selected to assume risks to evaluate a vaccine that will ultimately benefit children in developed countries (Weijer, written communication). As long as the RRV-TV vaccine would be made available to the population recruited for the study if proven safe and effective, children in the developing countries are being selected appropriately.[12,13,59]

The final element is evaluation of the risk-benefit ratio. In the United States, the RRV-TV vaccine posed a risk of intussusception of about 1 in 10 000, while rotavirus causes about 20 deaths annually or in fewer than 5 in 1 million children. Thus, in developed countries the risk-benefit ratio is not favorable—1 death from rotavirus diarrhea pre-

vented at the risk of 20 to 40 cases of intussusception. Because of underlying disease burden, the risk-benefit ratio in developing countries is much different. If rotavirus causes the death of 1 in 200 children while the RRV-TV vaccine causes intussusception in 1 in 10 000 children, about 50 deaths from rotavirus diarrhea are prevented for each case of intussusception. Consequently, the risk-benefit ratio of the RRV-TV vaccine is favorable for individual subjects in developing countries while it is unfavorable for subjects in developed countries. This difference in risk-benefit ratios is a fundamental part of the justification for conducting the research on an RRV-TV vaccine in a developing country when it could not be ethically conducted in a developed country (Weijer, written communication). Obviously, to be ethical, randomized controlled trials of an RRV-TV vaccine would also have to adhere to the other requirements—independent review, informed consent, and respect for enrolled subjects.

CONCLUSION

These 7 requirements for considering the ethics of clinical research provide a systematic framework to guide researchers and IRBs in their assessments of individual clinical research protocols. Just as constitutional rulings are rarely unanimous, this framework will not necessarily engender unanimous agreement on the ethics of every clinical research study. Reasonable disagreement results from 3 sources: differences of interpretations of the requirements, of views about the need for additional requirements, and of application to specific studies. Nevertheless, this framework does provide the necessary context for review bodies to generate traditions of interpretation, understand disagreements, and highlight the kinds of considerations that must be invoked to resolve them. Like a constitution, these requirements can be reinterpreted, refined, and revised with changes in science and experience. Yet these requirements must all be considered and met to ensure that clinical research—wherever it is practiced—is ethical.

Disclaimer: The views herein are those of the authors and do not represent the views or policies of the Department of Health and Human Services or the National Institutes of Health.

Acknowledgment: We thank Robert J. Levine, MD, Steven Joffe, MD, Franklin Miller, PhD, Robert Truog, MD, James Childress, PhD, Francis Crawley, PhD, and Albert Kapikian, MD, for their criticisms of the manuscript as well as Alan Sandler, DDS, Ruth Macklin, PhD, Eric Meslin, PhD, and Charles Weijer, MD, PhD, for helpful discussion and suggestions on the ideas contained in the manuscript.

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