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

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.