



# The New England Journal of Medicine

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Volume 341(7)

12 August 1999

pp 531-534

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## The Need to Revise the Declaration of Helsinki

[Sounding Board]

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### Outline

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The Declaration of Helsinki requires revision because it is defective in two important respects. First, it relies on a distinction between therapeutic and nontherapeutic research; all documents that rely on this spurious distinction contain errors not intended by their authors. [1] Second, it includes several provisions that are seriously out of touch with contemporary ethical thinking. As a consequence, many researchers routinely violate its requirements. Such routine violations and their associated attitudes rob the declaration of its credibility.

### Therapeutic and Nontherapeutic Research<sup>1</sup>

The nature of the errors that arise from a reliance on the distinction between therapeutic and nontherapeutic research is made clear by placing one of the document's provisions for therapeutic research (article II.6) next to one for nontherapeutic research (article III.2). [2]

II.6. The doctor can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III.2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

This pair of articles rules out all rational research on the causes of diseases or on their pathogenesis or pathophysiology. Consider, for example, research designed to explore the role of neurotransmitters in the pathogenesis of depression. Since this research cannot be justified on the basis of its therapeutic benefit for the patient, as required by article II.6, it must be considered nontherapeutic. Therefore, as required by article III.2, the subjects of the research must be either normal volunteers or patients who have diseases other than depression. This is what I mean by unintended errors.

The class of activities covered by the term "therapeutic research" is also problematic because all clinical trials of therapeutic agents include some components that may be therapeutic (or at least are so intended) and others that are clearly nontherapeutic. Those who rely on the distinction between therapeutic and nontherapeutic research usually categorize research protocols with one or more components that are intended to be therapeutic as therapeutic research. Thus, all components of such protocols, both therapeutic and nontherapeutic, are justified according to the relatively permissive standards for therapeutic research. Among the nontherapeutic interventions that have been justified on this basis are placebos, some of which have been administered by catheterization of the coronary artery, and repeated coronary angiography and endoscopy in patients who would not have undergone such procedures if they had been treated outside a research protocol. I refer to this phenomenon as the "fallacy of the package deal." [3]

It is because of such errors that in the 1970s, policy-making agencies in the United States and Canada rejected the distinction between therapeutic and nontherapeutic research. In his review of the major conceptual achievements of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in the 1970s, Jonsen gives pride of place to the repudiation of the false distinction between therapeutic and nontherapeutic research. [4] The commission recommended that this distinction be replaced by the much more satisfactory distinction made in the federal regulations for the protection of human subjects of research. [5]

The federal regulations, which are based on the commission's recommendations, require that each component of a research protocol be evaluated separately. An "intervention or procedure that holds out the prospect of direct benefit for the individual subject" is evaluated according to standards similar to those used to evaluate therapeutic procedures in clinical practice; practically any level of risk can be justified on the basis of the expectation of sufficient benefit to the subject. The risks of interventions or procedures that are not expected to provide benefit to individual subjects must be justified in terms of their intended benefit to society; the standards for such justification are much more exacting. For research involving children as subjects, for example, a nontherapeutic procedure that carries more than a minor increase over minimal risk must be reviewed at the national level.

## **Control Groups in Randomized Clinical Trials**

Provisions in the Declaration of Helsinki that govern the use of control groups pose several problems. Article II.3 states, "In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists." The requirement that all patients be assured of the best proven therapeutic method rules out the development of all new treatments except those for diseases for which there are no proven therapeutic methods. Article II.3 would have ruled out the withholding of belladonna and its derivatives in trials of histamine  $H_2$ -receptor antagonists for the treatment of peptic ulcer. Progress in the treatment of hypertension would have ended with a demonstration of the efficacy of ganglion-blocking drugs. These are examples of other unintended consequences of interpreting the Declaration of Helsinki literally.

Article II.3 has also been interpreted as meaning that the use of a placebo control is forbidden when there is a proven or a standard therapy. To examine the validity of this claim, separate analyses are needed for clinical trials in which the suspension of effective therapy would expose the subjects to a substantial risk of death or disability and those in which such unfavorable

outcomes would be highly improbable.

The use of placebo controls in the latter class of trials is relatively noncontroversial. Few knowledgeable commentators argue that clinical trials of new analgesics or antihistamines must have active controls. In such studies, any adverse effects of withholding an active agent are merely symptomatic and rapidly reversible if the subject finds them intolerable. Similarly, even in cases in which there is a remote possibility of a permanent injury, placebo controls are widely accepted if there are adequate safeguards against injury. Clinical trials of new antihypertensive drugs, for example, are generally placebo-controlled, and the subjects are patients with mild hypertension. Given the close monitoring that is characteristic of clinical trials, the probability of a serious complication, such as a stroke or myocardial infarction, in a patient with mild hypertension is very small. [6]

One justification for such practices is that they are responsive to the patient's right to self-determination. The Declaration of Helsinki recognizes the right of normal volunteers to assume risks that they consider reasonable in the pursuit of important new knowledge. Patients are also accorded such rights, but only for protocols designed to study diseases other than the ones with which the patients are afflicted. There is, then, no ethical justification for depriving patients of this right if they wish to contribute to the development of new knowledge about the diseases in which they are most interested - the diseases they have.

A second justification is grounded in considerations of efficiency. The use of active controls in low-risk trials would result in a substantial increase in expense as well as a loss of efficiency. In such trials the increased expense and decreased efficiency cannot be justified on the basis of the nearly negligible amounts of injury that would be prevented. The use of placebo can be evaluated as a procedure that presents either minimal risk or, at most, a minor increase over minimal risk. [6]

The Declaration of Helsinki was drafted by the World Medical Association during the period from 1953 through 1964. The paternalistic stance reflected in the sections on therapeutic research is consistent with the attitude of the medical profession in that era. [7] Moreover, the Council for International Organizations of Medical Sciences (CIOMS) states in *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, "The Declaration does not provide for controlled clinical trials." [8] Rather, it ensures the freedom of the physician "to use a new . . . therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering." In short, the declaration's provisions concerning therapeutic research are designed to cover the "compassionate use" of an investigational new drug, as is customary in clinical practice. [7]

In passing, it is worth noting that many medical journals routinely publish the results of placebo-controlled trials, thus apparently violating the standard set forth in article I.8 of the Declaration of Helsinki: "Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication."

Now let me turn to the much more controversial interpretation of the Declaration of Helsinki's position on the use of placebo controls - namely, that every patient in every country is entitled to receive the best proven therapy available in industrialized nations, even if such therapy is not available in the country in which the patient resides. This alleged entitlement was at the center of the most acrimonious controversy over the ethics of clinical trials in recent memory - the debate over the ethical justification of placebo-controlled trials of the "short-duration regimen" of zidovudine for the prevention of perinatal transmission of the human immunodeficiency virus

(HIV) in developing countries. [9-11]

The international ethical guidelines of the CIOMS speak most directly to the issues of multinational research. I have elsewhere compared the CIOMS guidelines with the Declaration of Helsinki and the Nuremberg Code. [12] According to guideline 8 in the CIOMS document, "The investigator must ensure that . . . the research is responsive to the health needs and the priorities of the community in which it is to be carried out . . . ."

The CIOMS document contains two additional criteria for ethical justification that may be considered corollaries to the standard of responsiveness. First, the data generated by the research must be relevant to the conditions that prevail in the host country. Second, the sponsors of the research must make a commitment in good faith to ensure that any therapeutic product developed in such trials will be "reasonably available" to the residents of the host country, if the product is found to be safe and effective.

The responsiveness standard and its corollaries make it clear that in some clinical trials it would be unethical to assure each subject that the best proven therapy would be made available, if that were understood to mean the best existing therapy in industrialized nations. Consider as an example the trials of the short-duration regimen of zidovudine in developing countries. Use of the 076 regimen (the common term for the standard treatment in developed countries, referring to the regimen used in AIDS Clinical Trials Group Protocol 076) as a control would have violated the above-stated requirement because developing countries have no need for information about whether the short-duration regimen is better or worse than the 076 regimen. For several reasons, most of which are economic, the 076 regimen cannot be made available to residents of developing countries on a continuing basis. What people in developing countries need to know is whether the short-duration regimen is better or worse than that which is currently made available to most of them (i.e., no antiretroviral therapy). This is exactly the kind of information one obtains from a placebo-controlled trial.

A new standard appears to be emerging for the required provision of therapy in clinical trials that are sponsored or cosponsored by agencies in developed countries and carried out in developing (host) countries. This standard, referred to as the "highest attainable and sustainable therapy," has been discussed in the course of developing documents to guide the conduct of multinational clinical trials. [13,14] The "highest attainable" therapy is the best therapy that one could reasonably provide under the conditions of the trial. The "highest sustainable" therapy refers to the level of therapy that one could reasonably expect to be continued in the host country after the trial has been completed. That is, there should be a reasonable expectation that the provision of the therapy could be sustained with the resources that would be available after the external support provided by the trial sponsors had been discontinued.

The standard of the highest attainable and sustainable therapy is intended to guide the selection of the agent to be administered as the control in a clinical trial - the regimen to be compared with the therapy that is being evaluated. The new standard is also designed to guide the selection of other therapies that are to be provided to subjects during the course of the trial as treatments for intercurrent infections or other diseases. All therapies that might influence the response to the therapy under evaluation would have to be considered in terms of whether they could continue to be provided. If not, then one would have to consider whether their provision might distort the conditions of the study to the extent that its results would not be relevant to the conditions in the host country.

Consider an example. In most of the countries in which the placebo-controlled trials of the

short-duration regimen of zidovudine for the prevention of perinatal transmission of HIV were carried out, women breast-feed their newborn infants. Women who know they have HIV infection do this even though it is known that breast-feeding can transmit the virus from mother to infant. [15] The health authorities in these countries advise women to breast-feed, for several reasons; one of the most important is the fact that infant formula is not available. Even if formula were available, there is no suitable supply of safe water with which to mix the formula. The odds that an infant would contract a lethal diarrheal syndrome from contaminated water might be even greater than the chance that the infant would die from HIV infection transmitted from the mother.

Now let us suppose that the researchers agreed to provide formula and purified water to all infants born to mothers enrolled in the trial of the short-duration regimen of zidovudine. It would be reasonable to predict that this single step would considerably reduce the rate of perinatal transmission of HIV among the study subjects. Unless the provision of formula and pure water could be sustained in the community after the research had ended, however, the data generated by the study would be of no relevance to the community in which the research had been carried out.

The 076 regimen (the best proven therapeutic method) entails prolonged oral administration of zidovudine to a pregnant HIV-infected woman, intravenous administration of zidovudine during delivery, and oral administration of the drug to the newborn infant. [16] The short-duration regimen that was evaluated in developing countries provides the same daily dose of zidovudine as the 076 regimen but for a much shorter period. That difference was responsive to one condition that prevails in the communities in which the trials were conducted - that is, pregnant women do not seek antenatal care until late in their pregnancies. Zidovudine was not administered intravenously during delivery because most medical facilities in the host communities lack the equipment needed to provide intravenous therapy. Finally, zidovudine was not provided to newborn infants because of the lack of a supply of safe water with which to mix it. All these conditions that dictated the design of the short-duration trials are related to economic factors in the developing countries.

It is also worth noting that the cost of the zidovudine in the 076 regimen is approximately \$800 per patient, or about 10 times the cost of the short-duration regimen. In the sub-Saharan countries in which some of the trials were carried out, the typical annual per capita allocation for health care is less than \$10. This is another reason to challenge the sustainability of the 076 regimen. The question of whether the short-duration regimen of zidovudine would be sustainable in some or all of the countries in which the trials were conducted is beyond the scope of this discussion. The idea that sustainability should be a criterion for the ethical justification of clinical trials was introduced into the discussion of ethical guidelines only after these trials had been terminated. The purpose of this discussion is to consider what guidelines should be in the future, not whether any particular trials in the past were ethically justified.

Critics of the trials of the short-duration regimen of zidovudine were concerned only about the lack of zidovudine for the control groups. Their arguments would have been more consistent if they had also insisted on the provision of all the other advantages in industrialized nations that set the context for the trial of the 076 regimen and its subsequent routine use for the prevention of perinatal transmission of HIV. In the absence of these advantages, it is impossible to implement the 076 regimen. Thus, in an important sense, the best proven therapeutic method includes the full complement of these advantages.

It is necessary to acknowledge with regret that there are great imbalances in the distribution of

wealth among the nations of the world. Developing countries that cannot afford all the goods and services to promote health care that are available to residents of industrialized nations must be allowed to develop treatments and preventive interventions that they can afford. Research sponsors, both industrial and governmental, in industrialized countries should not be prevented from assisting developing countries in their efforts in this regard. Interpretations of ethical codes and guidelines that force sponsors and investigators to distort their research protocols so that they are unresponsive to the needs of developing countries are detrimental to the interests of all concerned. The Declaration of Helsinki should be revised to reflect this understanding.

The revision of the Declaration of Helsinki must include the correction of the errors that I have noted. As a consequence of these errors, many researchers routinely violate the requirements of the declaration. The knowledge that investigators may ignore with impunity articles II.3 and III.2, for example, promotes the assumption that they may decide which of the document's other provisions they will observe and which ones they will ignore. Such routine violations and the attitudes associated with them tend to undermine the authority of the entire document.

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Supported in part by a grant (PO1 MH/DA 56 826-01A1) from the National Institute of Mental Health and the National Institute on Drug Abuse.

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*Accession Number: 00006024-199908120-00013*

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Version: rel5.1.0, SourceID 1.6412.1.133