Some Recent Developments in the International Guidelines on the Ethics of Research Involving Human Subjects[a]

ROBERT J. LEVINE[b]

Departments of Medicine and Pharmacology, Yale University School of Medicine, New Haven, Connecticut 06520, USA

ABSTRACT: We are in a period of reconsideration and revision of international ethical guidelines for the conduct of biomedical research involving human subjects. The proximate cause of much of this activity is the recent controversy over the ethics of the use of a placebo control in the clinical trials of the short-duration regimen of zidovudine for prevention of perinatal transmission of HIV infection, trials that were carried out in several so-called technologically developing countries. Critics of these trials claimed that they were in violation of Article II.3 of the Declaration of Helsinki, which 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 critics claimed that since the "best proven . . . method" is the 076 regimen, this is what must be provided to members of the control groups. Failure to do so, they asserted, was a serious breach of ethics. In response to this allegation, several major international and national agencies convened multidisciplinary groups to consider the ethics of multinational clinical research. The first thing they realized was that Article II.3 was in error in that it did not reflect contemporary ethical thinking. Moreover, it was routinely violated in research conducted in developed as well as in developing countries. What replaces this standard? The 1993 CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects include several criteria for justification of research carried out in developing countries. Most importantly, the research must be responsive to the health needs and priorities of the host country. They also require that any therapeutic products developed in such research must be made "reasonably available" to residents of the host country. A new standard is emerging for selecting therapies to be administered to participants in multinational clinical trials and for use as the control "treatment" in such trials. It is called the "highest attainable and sustainable" therapeutic method. Application of this standard differs from application of the "best proven method" standard in that it permits the evaluation of new therapies that are responsive to the health needs and priorities of resource-poor countries. It has long been recognized that the Declaration of Helsinki is a flawed document in that it relies on the illogical distinction between therapeutic and nontherapeutic research. This distinction has been removed from the most recent draft revisions of the Helsinki and the CIOMS documents.

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[b]Address for correspondence: Dr. Robert J. Levine, Departments of Medicine and Pharmacology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06520.

In the 1990s there has been a striking increase in interest in conducting multinational clinical trials. Most of this interest has been connected directly to the AIDS pandemic. Effective methods are needed urgently to treat patients who are already infected with HIV and to reduce the incidence of new infections.

Most of the clinical trials designed to deal with the AIDS problems in resource-poor countries are at least partially supported and carried out by sponsors and investigators from the industrialized countries. These trials necessarily are conducted in the resource-poor countries, with the inhabitants of these countries serving as research subjects.

Research involving human subjects must be conducted in compliance with legal and ethical standards. The recent increase in multinational collaborations has forced us to recognize that standards developed in the industrialized nations may not be applicable in the resource-poor nations. This recognition, in turn, has generated a high level of interest in developing international codes of ethics that are applicable to all regions in the world. A by-product of this project has been a growing recognition that the existing documents each have serious flaws that limit their applicability even in the countries in which they were developed.

It is often said that the AIDS pandemic has presented us with novel ethical problems that make it necessary to revise ethical codes and regulations for the protection of the rights and welfare of human research subjects. I disagree. I believe that most of the "novel" problems presented by AIDS have been there all along. Social and political features particular to the AIDS pandemic have forced us to pay attention to problems that should have been addressed long ago.[1]

Since World War II, three major international codes of research ethics have been developed: these are the Nuremberg Code, the World Medical Association's Declaration of Helsinki, and the International Ethical Guidelines for Biomedical Research Involving Human Subjects of the Council of International Organizations of Medical Sciences. A full discussion of each of these documents and their relation to each other is beyond the scope of this paper. (For a more complete discussion, see Levine.[2]) In this article I will concentrate on the Declaration of Helsinki because most critics of multinational clinical trials base their criticism on interpretations of this document.

THE DECLARATION OF HELSINKI

The Declaration of Helsinki was first promulgated by the World Medical Association at its meeting in Helsinki, Finland in 1964; subsequently, it has been amended several times.[2] I believe that the Declaration urgently requires revision.[3] I shall discuss the two most important reasons for my holding this belief: First, the Declaration is an illogical document. It categorizes all research as either "therapeutic" or "nontherapeutic"; every document that relies on this distinction contains errors — errors that are not intended by their authors and that, when exposed, often embarrass their authors. I shall provide some examples of such errors. Secondly, the Declaration is seriously out of touch with contemporary ethical thinking. For example, it takes an unnecessarily rigid stance against placebo-controlled clinical trials. Because of such errors, the Declaration is widely disregarded. Investigators in every academic medical center in the United States routinely do research that violates the standards es-

tablished by the Declaration. This widespread and routine disregard for the Declaration undermines its authority and credibility.

Therapeutic and Nontherapeutic Research

First, let us consider the distinction between therapeutic and nontherapeutic research. Section II of the Declaration sets forth the guidelines developed for therapeutic research; Section III is concerned with nontherapeutic research. Putting one article from Section II in immediate proximity with one from Section III helps elucidate the logical flaw:

> **II.6** The doctor can combine medical research with professional care...only to the extent that...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.

Let us consider what is ruled out by this pair of articles. They rule out all research in the field of pathogenesis, in the field of pathophysiology, and the entire field of epidemiology. Consider, for example, a recently published study that examines the role of neurotransmitters in the pathogenesis of mental depression. This study was nontherapeutic. It certainly could not be justified in terms of its potential diagnostic or therapeutic benefit to the patient. Therefore, according to the Declaration, it could only be done on normal volunteers or on patients who have some disease other than depression. This is what I mean by illogical and embarrassing.

The problems in the category of therapeutic research are equally troubling. The concept of therapeutic research is incoherent. At least some of the components of every research protocol are nontherapeutic; when they are all nontherapeutic, use of the term "nontherapeutic research" might be justified. When we evaluate entire protocols as either therapeutic or nontherapeutic, as required by the Declaration of Helsinki, we end up with what I call the "fallacy of the package deal." Those who use this distinction typically classify as "therapeutic research" any protocol that includes one or more components that are intended to be therapeutic; therefore, the nontherapeutic components of the protocol are justified improperly according to the more permissive standards developed for therapeutic research.

Such erroneous justifications in the recent past have included the following: in trials of thrombolytic therapy, repeated coronary angiograms on patients who had clinical indications for only one; liver biopsies performed for no reason other than to disguise treatment assignments in a double-blind, placebo-controlled trial; repeated endoscopies in a population of patients with peptic ulcers who had clinical indications for no more than one; and administration of placebo by way of a catheter inserted into the coronary artery. I do not want to be misunderstood as saying that any of these procedures was unethical. I am simply arguing that they should not be justified according to standards developed for "therapeutic research."

These examples illustrate the necessity for a vocabulary that enables the evaluation of these components of research. The United States and Canada, each recognizing the problems caused by the distinction between therapeutic and nontherapeutic research, purged these concepts from their regulations and guidelines in the 1970s. In the United States, in response to the recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

(National Commission), federal regulations were revised in the early 1980s to classify interventions and procedures—not entire protocols—as either beneficial or not.[4,5] In the language of the regulations for research involving children, interventions or procedures are classified as either those that hold out the prospect of direct benefit, or those that do not hold out such a prospect. They are referred to in the regulations as either beneficial or nonbeneficial. The justification of beneficial procedures is similar in principle to that employed in the practice of medicine. The intervention or procedure must hold out the prospect for the individual patient/subject of an improvement in his or her health. Moreover, in most cases there should be no other therapeutic procedure known to be superior to the one(s) being evaluated. There is no ceiling imposed on the degree of risk that may be imposed in the pursuit of therapeutic benefit—only that it must be reasonable in relation to the anticipated benefits.[5]

Obviously, nontherapeutic procedures cannot be justified in terms of their expected benefit for the patient/subject. They must be justified instead by the benefits one hopes to produce for society. The amount of risk that may be presented to vulnerable subjects by nonbeneficial procedures is limited by the so-called threshold standards in the regulations. For example, for research involving children, nonbeneficial interventions or procedures that present no more than minimal risk may be employed without special justification. Interventions and procedures that present only "a minor increase over minimal risk" must be justified on the grounds that the procedure itself "is likely to yield...knowledge...which is of vital importance for the understanding or amelioration of the subjects' disorder or condition," and "the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in [the subjects'] actual or expected medical...situations." Interventions or procedures that present more than a minor increase over minimal risk must be reviewed and approved at the national level.

Best Proven Therapeutic Method Standard

As I mentioned at the outset, the Declaration of Helsinki not only has logical flaws, but it is also out of touch with contemporary ethical thinking. This will be illustrated by considering Article II.3.

> 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.

Let us consider the implications of this article. This article would rule out the development of all new therapies for conditions for which there are already existing "proven" therapies. One cannot evaluate a new therapy unless you withhold those that have already been demonstrated safe and effective for the same indication. Strict application of this standard would have prevented the evaluation of the effectiveness of cimetidine and other H2 receptor antagonists for the treatment of peptic ulcer because the withholding of belladonna and its derivatives would have been considered an unethical withholding of the "best proven therapeutic method." Similarly, the development of new and improved antihypertensive drugs would have ceased with the establishment of the ganglionic blockers. This is also an illustration of what I mean by embarrassing.

Article II.3 also forbids placebo controls in clinical trials in which there is virtually no risk from withholding proven therapy. Consider research in the field of analgesics and antihistamines. No experienced person would ever recommend that you are required to have an active control in the evaluation of a new analgesic. Article II.3 also rules out the use of placebo controls in clinical trials in which there is a very remote possibility of an adverse consequence of withholding the active drug, such as trials of new antihypertensives and of new oral hypoglycemic agents. Insisting on active controls in these areas would introduce major inefficiencies in the research enterprise without much compensating benefit; the amount of injury to research subjects that would be prevented by requiring active controls is so small that it can be and generally is considered negligible.

Placebo-controlled trials of analgesics, antihypertensives, and oral hypoglycemics are conducted commonly, and the results are published in medical journals. Parenthetically, it is worth noticing that such publication is yet another routine violation of Helsinki; Article I.8 holds that "reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication."

Now let us turn to the most controversial interpretation of Article II.3, that this Article requires the provision of the best proven therapeutic method that is available in the industrialized countries even when conducting research in countries in which such therapy is not available. This interpretation has provoked the most acrimonious debate in in the field of research ethics since the 1970s. The debate was begun with the publication in *The New England Journal of Medicine* of an article that denounced as unethical the clinical trials that were being carried out in certain developing countries to evaluate the effectiveness of the short-duration regimen of AZT in preventing perinatal transmission of HIV infection.[6] The editor of the *New England Journal* opined that these trials were, in certain respects, reminiscent of the notorious Tuskegee syphilis studies[7]; this is, in contemporary American culture, one of the most powerful metaphors for symbolizing evil in the field of research ethics. The other side of the controversy is exemplified by a statement of a physician-researcher from Uganda, one of the countries in which the trials were conducted. He accused the editor of a form of "ethical imperialism" that asserts that the Western vision of research ethics must dominate the conduct of research everywhere in the world.

Let us consider this clinical trial in some detail as a case study. At the time the trial began, and indeed to this day the standard in industrialized countries like the United States, is the so-called 076 regimen. The name comes from ACTG protocol number 76, the AIDS Clinical Trial Group protocol that established its safety and efficacy. The 076 regimen reduces perinatal transmission of HIV infection by about 67%; the cost of the chemicals alone for treating each infected pregnant woman was, in 1997, about $800. Why can't we just provide the 076 regimen to women infected with HIV in the developing countries? First and foremost is the cost. Eight hundred dollars per woman is approximately 80 times the annual per capita health expenditure in many of the sub-Saharan African countries in which these trials were carried out. The cost of the chemicals is not the only problem; there are several other obstacles, most of which are also related to finances. I shall name some of the others. (For a more complete discussion of these problems, see Ref. 8.)

Provision of the 076 regimen would also have required a revision of the customs within the host countries for seeking prenatal care. In most of these countries, wom-

en simply do not consult a health-care professional early enough in pregnancy to begin the regular 076 regimen. It would also have required intravenous administration of AZT during delivery; in most regions of the host countries, no facilities exist for the intravenous administration of anything. And finally, in the host countries for these trials, with the exception of Thailand, women breastfeed their newborn babies even when they know they have HIV. The risk to the babies of providing them with any available alternatives to breastfeeding may be even greater than the risk of exposing them to infection with HIV through breastfeeding. The transmission rate of HIV infection by way of breastfeeding is about 14%. But in the regions in which the "short-duration" regimen of AZT was evaluated, particularly in sub-Saharan Africa, the death rate from infant diarrheal syndromes is about 4 million per year. In these countries, there is no infant formula. We could make the infant formula available in these countries, but that would not help. One cannot mix the formula with the local water supply because it is contaminated with, among other things, the pathogens that cause the deadly infant diarrheal syndrome.

To sum up: It is clear that the 076 regimen of AZT cannot be made available to most HIV-infected pregnant women in the resource-poor countries now or in the forseeable future. This is the main reason that it is essential to find methods to reduce the rate of perinatal transmission of HIV that are within the financial reach of the resource-poor countries. That was the primary justification for conducting the clinical trials of the short-duration regimen of AZT. The cost of the AZT in this regimen was about 10% of that of the 076 regimen. Moreover, there was no need for intravenous therapy or administration of the drug to the babies. At the time the trials began, it seemed likely that two of the countries could afford to provide the short-duration regimen if it proved effective; there was also a commitment from international agencies to assist the other resource-poor countries in securing and providing the drug.

Now let us consider whether the best proven therapeutic method standard for a clinical trial should be construed to mean the best therapy available anywhere in the world or the standard that prevails in the host country. Guidance on this point can be found in another document—the International Ethical Guidelines for Biomedical Research Involving Human Subjects—a document prepared by the Council of International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO). This document, which (unlike any other international document) explicitly addresses the problems of multinational research, offers some guidelines that I believe are far superior to informed consent and other traditional protections in preventing the exploitation of people in developing countries. First, for any research that is sponsored by an agency in an industrialized country and carried out in a developing country: the research goals must be responsive to the health needs and the priorities of the host country or community. Secondly, it requires that any product developed in the course of such research must be made reasonably available to the inhabitants of the host country. This then focuses multinational research on the needs of the country in which the research is carried out. No more conducting phase I drug studies in Africa simply because it's less expensive and less vigorously regulated.

CIOMS also provides some commentary on the problem with the Declaration of Helsinki: "[T]he Declaration does not provide for controlled clinical trials. Rather, it assures the freedom of the physician 'to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or

alleviating suffering' (Article II.1). Also in regard to Phase II and Phase III drug trials, there are customary and ethically justified exceptions to the requirements of the Declaration of Helsinki. A placebo given to a control group, for example, cannot be justified by its 'potential diagnostic or therapeutic value for the patient,' as Article II.6 prescribes."

In my analysis, the initiation of a research program cannot be considered the same as the establishment of an entitlement to the best therapy that is available anywhere in the world.[8] Secondly, the relevant standard is the one that prevails in the host country.[8] I think it would be improper to withhold anything that is generally available in the host country in order to do research designed to evaluate something else.

THE HIGHEST ATTAINABLE AND SUSTAINABLE THERAPEUTIC METHOD

A new ethical standard is now emerging on the international research ethics scene. This standard is called the "highest attainable and sustainable therapeutic method" standard. This ungainly name requires some explanation: "highest attainable" means that under the circumstances of the clinical trial, the level of therapy one should provide should be the best one can do. The level of therapy that is generally available in the host country should not necessarily be considered sufficient; rather, it should be considered a minimum—the least that might be considered ethically acceptable.

"Sustainable" means a level of treatment that one can reasonably expect to be continued in the host country after the research program has been completed. It is a level of treatment that the host country can reasonably be expected to maintain relying only on its own resources when the extra resources provided by sponsors from industrialized countries are no longer available.

"Sustainability," then, serves as a constraint on "highest attainable." One should provide the highest level of therapy that one can under the circumstances of the clinical trial; however, one should keep in mind that if the level of therapy is not sustainable, the results of the trial may not be responsive to the needs and priorities of the host country and the therapeutic product developed in the research program may not be reasonably available to inhabitants of the host country. A very important consideration is that provision of a therapy that is not sustainable may distort the research setting to the extent that the results may not be applicable in the host country.

The "highest attainable and sustainable therapeutic method" standard is reflected in the near-final draft of the UNAIDS Guidance Document for the conduct of multinational trials of HIV prevention vaccine and in the current draft of the revision of the CIOMS International Ethical Guidelines. A closely related standard is reflected in the current draft revision of the Declaration of Helsinki.

The "highest attainable and sustainable therapeutic method" standard applies to selecting therapies that are to be evaluated in resource-poor countries and also to selecting some of the treatments that would be made available to subjects in the course of conducting the clinical trials. To illustrate the latter application, let us consider a clinical trial of a new HIV-preventive vaccine that is to be carried out in a resource-poor country. It is assumed that such a vaccine will not prevent infection. Rather, one hopes that it will prevent or retard the progression from infection to the development

of clinical disease. Thus, in a field trial of such a vaccine, the primary outcome measure is likely to be some manifestation of disease resulting from HIV infection.

Now let us further suppose that at the time this trial is initiated, the standard of care in industrialized countries is to administer a course of antiretroviral drugs to health-care workers who have occupational exposures to HIV—a treatment known as post-exposure prophylaxis (PEP). And let us further suppose that in the context of the vaccine trial one could use antiretroviral drugs for the purpose of PEP. However, the cost of such PEP would ensure that it could not be sustained after the vaccine trial was concluded. Is it morally obligatory to provide PEP to participants in the vaccine trial?

PEP could be required ethically if the criterion were only "highest attainable." However, because PEP is not sustainable, it would appear that it is not ethically required. The practical implications should also be mentioned. If PEP were provided to subjects in the vaccine trial and if it were highly effective in preventing progression of HIV infection to disease, there would be so few "primary outcomes" that one might never learn whether the vaccine is effective. Or if it were merely moderately effective in delaying progression to disease, it would be highly questionable whether the data derived from the vaccine trial were truly relevant to disease prevention in the country in which the trial was conducted.[9]

The reason that provision of antiretroviral PEP is not morally obligatory is related primarily to its lack of sustainability and not merely because it might reduce the efficiency of the trial by decreasing the number of outcome events. Counseling research subjects about reducing behaviors that increase their risk of HIV infection would similarly, if effective, reduce the efficiency of vaccine trials by decreasing the number of outcome events. However, because counseling can be sustained even in resource-poor countries after the vaccine trials have been completed, it is generally required ethically to provide counseling during the course of vaccine trials.

Those who insist that Helsinki Article II.3 must be interpreted as requiring the provision of the best proven therapeutic method that is available in industrialized countries even when research is carried out to address the needs of resource-poor countries must understand the implications of this position. To consider once again our case study—the trials of the "short-duration AZT regimen" in preventing perinatal transmission of HIV—most resource-poor countries cannot even afford to purchase sufficient AZT to implement the best therapeutic method (the 076 regimen). In order to truly provide the "best," it is also necessary to provide all of the other advantages that exist in industrialized countries that enable the 076 regimen to be effective. These include, among other things, infant formula as an alternative to breastfeeding, a water supply that is safe for infants, and the facilities for intravenous administration of drugs. All of these "advantages," taken together, would cost far more than the AZT. Clearly the cost of the 076 regimen is beyond the reach of most of the resource-poor countries. Insistence on this standard would accomplish nothing other than to deny to resource-poor countries the possibility of developing therapies and preventions that they can afford. Moreover, it would preclude the participation of sponsors and investigators from industrialized countries in research and development programs designed to assist the resource-poor countries in developing affordable treatments and preventions.

Application of the "highest attainable and sustainable therapeutic method" standard is, in all relevant respects, a more suitable ethical standard. One of its chief ad-

vantages is that it tends to facilitate the efforts of resource-poor countries to develop needed therapies and preventions that are within their financial reach. Until the imbalances in the distribution of wealth among the nations of the world are corrected, this appears to be the best we can do.

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9. This is necessarily an overly simplistic analysis of the justification of PEP. A thorough ethical analysis would entail taking into account all of the ethical standards embodied in (e.g.) the UNAIDS Guidance Document. Such an analysis is far beyond the scope of this article.