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International Codes and Guidelines for Research Ethics: A Critical Appraisal

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This chapter is concerned with international codes and guidelines that offer guidance for the ethical conduct of research involving human subjects.[1] The major documents to be considered are the *Nuremberg Code*, the World Medical Association's (WMA) *Declaration of Helsinki*, 1964 and 1975, and *The International Ethical Guidelines for Biomedical Research Involving Human Subjects* developed by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO); these will be referred to respectively as *Nuremberg*, *Helsinki*, and *CIOMS Guidelines*.

There is a continuing controversy as to which, if any, of these three documents should be considered most authoritative in cases of inconsistencies. This paper will not refer further to this controversy. At this point I shall simply state my perspective on this issue; evidence to support this perspective will be presented subsequently. I believe these international documents should be considered a progression with each succeeding document superseding its precursors. Those who wrote *Helsinki* and *CIOMS Guidelines* were aware of the work of their predecessors. To a considerable extent they found their predecessors' work very useful and drew heavily on their accomplishments. But also, they each found the work of their predecessors imperfect or incomplete and were motivated to a large extent to correct the imperfections or supply the deficiencies they detected.

The authors of *Helsinki* were concerned with the fact that *Nuremberg* did not provide adequate guidance for most of the

research activities carried out by medical doctors using humans as research subjects. Thus, they found it necessary to add provisions for authorization by proxy consent of the use of children and others lacking the capacity to consent for themselves. It was also necessary to provide guidance for the conduct of research in which risk could be justified by expected therapeutic benefit to the individual subject and not solely "by the humanitarian importance of the problem to be solved by the experiment" (*Nuremberg*, principle 6 in this book's Appendix A).

The *CIOMS Guidelines* explicitly acknowledge the influence of *Nuremberg* and *Helsinki*. Indeed, *CIOMS* quite modestly states that its guidelines are designed to provide guidance for the correct application of the principles of *Helsinki*, particularly when research is initiated by researchers and sponsors in technologically developed countries and carried out in developing countries. However, as we shall see, the *CIOMS Guidelines* clearly depart from *Helsinki's* requirements in several substantial respects. Justification of these departures are offered at several points. For example, "the Declaration [of Helsinki] does not provide for controlled clinical trials. Rather, it assures the freedom of the physician 'to use a new diagnostic or therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.' "[2]

In this chapter, I shall examine the continuing controversy between adherents to the position of ethical universalism and those committed to the position of cultural pluralism. As we shall see, the authors of *Nuremberg* and *Helsinki* each believed that their documents were universally applicable. Each asserted principles that they intended and earnestly believed to be universal. I shall present evidence to refute these claims of universal validity. I shall argue that the *CIOMS Guidelines* are more successful than their predecessors in reaching global applicability.[3] Their success may be attributed to two of their accomplishments: First, unlike *Nuremberg* and *Helsinki*, they recognize the legitimacy of a limited degree of cultural pluralism. Second, the *CIOMS Guidelines* avoid *Nuremberg's* errors of omission and *Helsinki's* logical imperfections. The chapter concludes with recommendations for future efforts to improve international guidelines for the ethical conduct of research involving human subjects.

ETHICAL UNIVERSALISM OR PLURALISM?

In the course of the recent international dialogue on healthcare, ethics, and human rights it has become increasingly clear that some participants in the dialogue are firmly committed to ethical universalism and some others to ethical pluralism.[4] Ethical universalists believe there is a universal set of ethical principles that are applicable to all human beings regardless of their situations in particular cultures. The task of the moral philosopher, then, is to discover those universal principles that apply in all times and in all places. Ethical pluralists, by contrast, recognize that all ethical principles are developed in the course of discussions held within particular cultures and that these discussions necessarily reflect the unique histories and other circumstances of particular cultures. On this view, ethical principles are invented rather than discovered. Pluralists further acknowledge the inevitability and recognize the legitimacy of variation across cultures of ethical norms and principles. In recent years, participants in the debate have engaged in name-calling with pluralists labeling universalists "ethical imperialists," and universalists branding pluralists "cultural relativists."

CLAIMS OF UNIVERSALITY IN THE INTERNATIONAL DOCUMENTS

Michael Grodin concludes his important article on the historical origins of *Nuremberg* by calling it "an attempt to provide a natural law based on a universal set of ethical principles."[5] That this vision was shared by *Nuremberg's* authors is indicated by the judges' statement in its preface: "*All* agree, however, that certain basic principles must be observed in order to satisfy moral, ethical and legal concepts" (emphasis added). Immediately following this sentence are the 10 principles of the code. Another statement by the judges, which follows the principles, further reflects their belief in the universality of the principles:

> Obviously all of these experiments . . . were performed in complete disregard of international conventions, the laws and customs of war, the general principles of criminal law as derived from the criminal laws of all civilized nations. . . . Manifestly, human experiments under such

conditions are contrary to 'the principles of the law of nations as they result from the usages established among civilized peoples, from the laws of humanity, and from the dictates of public conscience.'[6]

This statement grounds the argument advanced by some commentators that the authors of *Nuremberg* considered it a natural law document.[7]

Helsinki asserts its claim to universality in its introduction by reference to two other documents: "The Declaration of Geneva of the World Medical Association *binds the physician* with the words, 'The health of my patient will be my first consideration,' and the International Code of Medical Ethics declares that, 'A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient' " (emphasis added; see Appendix B of this book for the *Helsinki Code*). Later in the introduction, *Helsinki* refers to its "recommendations as a guide to *every physician* in biomedical research involving human subjects" (emphasis added).

In the *CIOMS Guidelines*, immediately preceding the preamble, there is a passage entitled "General Ethical Principles." These are the familiar "basic ethical principles" first introduced into a public policy context in the United States in 1978 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research: respect for persons, beneficence, and justice. At no point in the guidelines is there any further reference to these principles.

Because *CIOMS Guidelines* are particularly concerned with research carried out by investigators from developed countries involving as subjects residents of developing communities, its authors were obliged to come to terms with cross-cultural variations in ethics. Like *Nuremberg* and *Helsinki*, the *CIOMS Guidelines* also aspire to worldwide applicability. However, unlike *Nuremberg* and *Helsinki*, they do not assert the universal validity of a set of rules that either prescribe or proscribe specific behaviors. Rather, they recognize the legitimacy of a limited amount of ethical pluralism. According to the commentary under guideline 8: "Investigators must respect the ethical standards of their own countries and the cultural expectations of the societies in which

the research is undertaken, *unless this implies a violation of a transcending moral rule*" (emphasis added).

The *CIOMS Guidelines*, unlike *Nuremberg* and *Helsinki*, recognize that certain behaviors that are ethically acceptable in one cultural context may be unacceptable in another. They recommend procedures that may be followed to reach agreements about what types of behavior would be considered ethically acceptable in cases in which the norms of the investigators' culture differ from those of the host country. In the commentary on guideline 15, CIOMS states that: "[E]thical review in the external sponsoring country may be limited to ensuring compliance *with broadly stated ethical standards,* on the understanding that ethical committees in the host country will have greater competence in reviewing the detailed plans for compliance in view of their better understanding of the cultural and moral values of the population in which the research is proposed to be conducted" (emphasis added).

Reasons for this recommendation are elaborated further in the commentary under guideline 8:

> The *ability to judge* the ethical acceptability of various aspects of a research proposal requires a *thorough understanding of a community's customs and traditions.* The ethical review committee must have as either members or consultants persons with such understanding, so that the committee may evaluate proposed means of obtaining informed consent and otherwise respecting the rights of prospective subjects. Such persons should be able, for example, to identify appropriate members of the community to serve as intermediaries between investigators and subjects, to decide whether material benefits or inducements may be regarded as appropriate in the light of a community's gift-exchange traditions, and to provide safeguards for data and personal information that subjects consider to be private or sensitive (emphasis added).

ARE THE INTERNATIONAL DOCUMENTS GLOBALLY OR UNIVERSALLY APPLICABLE?

Nuremberg is clearly an American creation. As stated by Telford Taylor in the opening statement of the prosecution on 9 December 1946: "The charges against these defendants are brought in the name of the United States of America. They are being tried by a court of American judges."[8] In drafting the *Nuremberg Code*,

the judges relied heavily on the testimony and advice of two American physicians who were also experienced researchers, Andrew Ivy and Leo Alexander. Indeed, major portions of the final document were drafted by these two consultants.[9]

In passing, it is worth noticing that in the United States, in recent years, any policy-making body comprised exclusively of white, upper middle-class men would be regarded as highly suspect, even if its mandate were limited to determining real estate zoning rules. In the late 1940s, by contrast, such homogeneously male and white groups commonly issued pronouncements on what could be considered proper behavior for all "civilized people." This is not to say that *Nuremberg* is necessarily incorrect in any respect merely because only white American men participated in its conception. One wonders, however, just whom might they have considered "uncivilized."

Doctors Ivy and Alexander relied on resources that they believed elaborated universally applicable ethical principles. These included the Oath of Hippocrates, which they quoted incorrectly in at least two respects: First, they said it was the source of the dictum commonly regarded as the first principle of medical ethics, *primum non nocere* (first, or above all, do no harm). The closest approximation of such a statement in the Hippocratic writings is found in *Epidemics*: "As to diseases, make a habit of two things–to help, or at least to do no harm."[10] Second, they strongly implied that the oath of Hippocrates covered the ethics of research involving human subjects, although research is not mentioned either in the oath or anywhere else in the Hippocratic corpus. Other authorities on whom they relied either implicitly or explicitly were all writers situated in the tradition of Western civilization including Thomas Percival (British), William Beaumont (American), Claude Bernard (French), and several pre-World War II German writers.[11] Alexander also cited several American reviews and court decisions as important grounds for his ethical perspectives.[12]

An even more serious problem was that the consultants, particularly Ivy, attempted to convince the judges that the principles they were recommending–and that became the *Nuremberg Code*–were already employed to guide the conduct of research involving human subjects in the United States and elsewhere in

the "civilized world." This is clearly an error. With the possible exception of Andrew Ivy himself, I am aware of no investigator (myself included) who was actively involved in research involving human subjects in the years before 1964 who recalls any attempts to secure voluntary or informed consent according to *Nuremberg's* standards.[13] Normal volunteers were usually advised that they were being asked to participate in research, and there was usually a presentation of the major risks and in some cases, particularly for the more intelligent or curious, the intended benefits. Patients, however, were rarely advised if and when some additional procedures that were not clinically indicated were performed to serve the goals of research, even when these presented non-trivial risks.

According to Grodin, Ivy attempted to mislead the tribunal by giving false testimony about the ethical standards that were in place in the United States at the time the Nazi experiments were performed:

> It appears that Dr. Ivy studied the tribunal prosecution's pretrial records and exhibits and then reported his views on the ethics of human experimentation to the American Medical Association's trustees, who *subsequently* incorporated his guidelines into the *Journal of the American Medical Association*. . . . In cross examination, the defense readily discovered the lack of . . . published substantive standards on human experimentation in the United States . . . prior to 1946. [emphasis added][14]

This point notwithstanding, the standards to which Ivy referred were, with some alterations, incorporated into the *Nuremberg Code*.

At this point it should be clear that *Nuremberg* is not an accurate account of standards that can be accepted as universal regardless of the intentions of its authors. Let us now consider *Helsinki*. Sharon Perley and her colleagues have published a comprehensive overview of the influence of the *Nuremberg Code* on subsequent development of international and national guidelines for the conduct of research involving human subjects.[15] They provide convincing evidence that *Nuremberg*, though nowhere mentioned in the *Declaration of Helsinki* or any of its early drafts, "greatly influenced" the development of the declaration. "Although nowhere documented, this . . . conclusion has been

reached by almost all commentators [on] medical research ethics."[16]

In 1953, the World Medical Association's Committee on Medical Ethics began its discussion of the problems presented by medical research. At that time, it recognized

> a need for *professional* guidelines designed *by physicians for physicians* (as opposed to the *Nuremberg Code*, which was formed by jurists for use in a legal trial). Moreover, it was recognized that experiments must be classified into two groups: "experiments in new diagnostic and therapeutic methods" and "*experiments undertaken to serve other purposes than simply to cure an individual.*"[emphasis added][17]

As will become clear shortly, it is the second of these two recognitions that led to the development of a major flaw in *Helsinki*, an error in logic that undermines its validity in any time or place. Therefore, there is little need to examine in detail its claim to universality. It is, however, worth considering briefly some similarities and differences between *Nuremberg* and *Helsinki*.

Perhaps because the writing of *Helsinki* was "greatly influenced" by *Nuremberg*, it continues to require consent for the authorization of research involving each and every individual subject; in this way it continues the American perspective.[18] While *Nuremberg* referred to "voluntary consent," with "informed" being one of its elements, *Helsinki* calls it "informed consent." Unlike *Nuremberg*, *Helsinki* recognizes the validity of proxy consent in situations in which the subject lacks the capacity or legal competence to consent. Alexander had proposed to the judges at Nuremberg that they include provisions for consent by the next of kin for "mentally sick patients"; they declined "probably because they did not apply to the specific cases under trial."[19]

As mentioned earlier, *Nuremberg* seemed to have little or no influence on the actual conduct of research even in the United States, the nation that instigated its promulgation. By contrast, publication of *Helsinki* in 1964 effected change almost immediately. Shortly thereafter, investigators found that, on the occasion of submitting abstracts of their work for consideration for presentation at conventions such as those of the American Federation for Clinical Research, they were obliged to sign statements that their work had been conducted in accord with the *Declaration of Helsinki*. Similar statements were required of authors when they submitted reports of their work for publication in medical or scientific journals.

In the United States, the first federal policy statement on the protection of human subjects was issued by the Surgeon General of the United States Public Health Service on 8 February 1966, less than two years after promulgation of *Helsinki*.[20] In the same year, Henry Beecher's classical exposé, "Ethics and Clinical Research," was published in the *New England Journal of Medicine*.[21] I believe that the availability of a document that set forth specific criteria for ethical justification of research involving human subjects enabled Beecher and others who published exposés in the late 1960s and early 1970s to do so. For the first time, there was an official document created by physicians and endorsed by many medical organizations to use as a measuring stick. Now one could state, "This is a violation of article I.5 of *Helsinki*," rather than, "I think this is wrong because it allows the interests of science and society to prevail over those of the subjects."[22]

As noticed earlier, *Nuremberg* may reflect an excessively American bias owing to the composition of the group that wrote it. *Helsinki* was drafted by a committee of physicians who recognized a need for professional guidelines designed by physicians for physicians. This may account for its focus on assuring that physicians have the freedom to use new therapeutic and diagnostic modalities if, in their judgment, they offer important advantages over standard therapeutic and diagnostic measures. It may also account for the fact that, even in its most recent revision in 1989, *Helsinki* does not require approval by a research ethics committee.[23]

The group that developed the *CIOMS Guidelines* was distinctly heterogeneous with regard to gender, race, nationality (both developed and developing countries) and profession ("representatives of ministries of health and medical and other health-related disciplines, health policy makers, ethicists, philosophers and lawyers").[24]

The *CIOMS Guidelines* come closer to global validity than did its predecessors. There is, for example, a distinct departure from the uniform requirement for informed individual or proxy consent based on recognition that in some cultures individual informed consent cannot be accomplished. There is, moreover, a

systematic repudiation of the illogical constructs that undermine the validity of *Helsinki*. And yet, as I shall discuss shortly, more work needs to be done to make this document even more widely applicable.

THE PROBLEM OF EXPLOITATION

Universalists argue that there must be universal standards to prevent exploitation of residents of technologically developing countries. Universalists correctly point out that most therapeutic innovations are developed in industrialized nations. Investigators from these countries may go to technologically developing countries to test their innovations for various reasons. Some of these reasons are good (for example, some of the diseases for which they wish to develop therapies exist only or primarily in developing countries), and some of them are not (for example, to take advantage of the less complex and sophisticated regulatory systems typical of developing countries). Moreover, universalists observe that once the innovations have been proven safe and effective, economic factors almost always limit their availability to citizens of the country in which they were tested. Requiring investigators to conform to the ethical standards of their own country--or to those embodied in the *Declaration of Helsinki*--when conducting research abroad is one way to restrain exploitation of this type. Universalists also point to *Helsinki* as a widely accepted universal standard for biomedical research that has been endorsed by most countries, including those labeled technologically developing. This gives weight to their claim that research must be conducted according to universal principles. Furthermore, the complex regulations characteristic of technologically developed countries are, in general, patterned after *Helsinki*.

Marcia Angell, in a particularly incisive exposition of the universalists' position, suggests this analogy:

> Does apartheid offend universal standards of justice, or does it instead simply represent the South African custom that should be seen as morally neutral? If the latter view is accepted, then ethical principles are not much more than a description of the mores of a society. I believe they must have more meaning than that. There must be a core of human rights that we would wish to see honored universally, despite local variations in their superficial aspects. . . . The force of local custom or law cannot justify abuses of certain fundamental rights, and the right of self-determination, on which the doctrine of informed consent is based, is one of them.[25]

Pluralists join with universalists in condemning economic exploitation of technologically developing countries and their citizens.[26] Unlike the universalists, however, they see the imposition of ethical standards for the conduct of research by a powerful country on a developing country as another form of exploitation. In their view, it is tantamount to saying: No, you may not participate in this development of technology, no matter how much you desire it, unless you permit us to replace your ethical standards with our own. Pluralists call attention to the fact that *Helsinki*, although widely endorsed by the nations of the world, reflects a uniquely Western view of the nature of the person. As such, it does not adequately guide investigators in ways to show respect for all persons in the world.[27]

Pluralists argue that it is unnecessary to assert the universal validity of specific substantive standards. The issue of how to treat persons with respect, for example, is not resolved by insisting on universal requirements for informed consent. It is better to address this issue as has been done in the *CIOMS Guidelines* through the promulgation of "broadly stated [international] ethical standards" with the expectation that the details of compliance with these broadly stated standards will be worked out on a case-by-case basis by ethical committees in the host country that have a high degree of understanding of what it means to treat a person with respect in the community in which the research is to be conducted.

The problem of exploitation of developing countries may also be dealt with satisfactorily, as has been done in *CIOMS Guidelines*. In guideline 8, for example, there is a prohibition against undertaking research involving subjects in underdeveloped communities unless, (1) it could not be carried out reasonably well in developed communities and, (2) the research is responsive to the health needs and priorities of the community in which it is to be carried out. There are several additional requirements specified to minimize the likelihood of exploitation of developing communities and their individual members. In particular, the

CIOMS Guidelines require review *and approval* of all proposed research by ethical review committees in both the initiating and the host countries, while *Helsinki*, article I.2, requires only "consideration, comment and guidance" by an independent committee "in the country in which the research experiment is performed." *Nuremberg* is silent on the matter of ethical review, placing all responsibility for upholding ethical standards on the investigator.

Moreover, *CIOMS Guidelines* include detailed accounts of the responsibilities of research sponsors including pharmaceutical companies and other institutions to assure, for example, "that any product developed through . . . research will be made reasonably available to the inhabitants of the host community or country at the completion of successful testing. Exceptions to this general requirement should be justified and agreed to by all concerned parties before the research begins" (commentary under guideline 15).

THE RELEVANCE OF EMPIRICAL DATA

Although the tension between universalism and pluralism is not likely to be resolved soon, there is one point on which adherents to each of these positions can and do agree. Any attempt to develop guidelines for ethical conduct must be grounded in a thorough and accurate understanding of the culture or cultures in which the guidelines are to be applied; otherwise, the guidelines will not accomplish their objectives. In an article in which they question the validity of the first set of international guidelines promulgated by CIOMS in collaboration with WHO, *Proposed International Guidelines for Biomedical Research Involving Human Subjects*,[28] IJsselmuiden and Faden recognize the importance of a thorough understanding of the cultures that will be affected by guidelines.[29] However, they claim that virtually all recent commentary on research ethics in developing countries, particularly those in Africa, relies on anthropological data that are out of date. For this reason they challenge the reliability of many recommendations offered by recent commentators–especially those who endorse informed consent policies and practices in developing countries that differ from those prevailing in developed countries as do the *CIOMS Guidelines*.

The anthropological studies IJsselmuiden and Faden characterize as "outdated" were published as recently as the 1980s. IJsselmuiden and Faden claim that such studies become obsolete so rapidly largely owing to the extensive recent "urbanization, education and industrialization" of the African population. Their claim is at odds with one conclusion reached by the symbolic anthropologist, Emiko Ohnuki-Tierney, based upon her field studies in modern urban Japan. Ohnuki-Tierney's data afford a convincing refutation of the assumption that modernization or urbanization undermines the symbolic realm of the people, the structure of their meaning and thought.[30]

THEORETICAL CONSIDERATIONS

Ruth Macklin argues:

> Something is amiss if ethical theory allows only . . . two alternatives: an ethical relativism that reduces to radical subjectivism, an 'anything goes' morality; or an ethical absolutism that posits the existence of moral commands obligatory for everyone, but neither universally acknowledged nor clearly articulated. I think there is an alternative to these two unacceptable philosophical positions. One way of spelling out that alternative lies in an analysis of the concept of moral progress.[31]

Macklin argues that unless we have some "basic normative principles," we can make no judgments as to whether our society advanced or regressed when we, for example, abolished slavery or accorded to women the right to vote. Moreover, we have no basis for saying whether a society that tolerates apartheid or torture of prisoners is more or less "advanced" in a moral sense than one that does not. Agreement on such basic normative principles "does not require a prior acceptance of some particular absolutist ethical theory . . . to make cross-cultural or transhistorical judgments about comparative degrees of moral progress.[32]

Macklin proposes two basic normative principles, *humaneness* and *humanity*:

> *Humaneness*: One culture, society, or historical era exhibits a higher degree of moral progress than another if the first shows more sensitivity to (less tolerance of) the pain and suffering of human beings than does the second, as expressed in the laws, customs, institutions, and practices of the respective societies or eras.

Humanity: The more advanced society would show "more recognition of the inherent dignity, the basic autonomy, or the intrinsic worth of persons."[33]

Macklin makes it clear that these basic normative principles, indeed even "ultimate moral principles," can be compatible with very different normative standards in different societies. In fact, interpretation of the same basic principle can give rise to rules calling for opposite behaviors in two societies that differ in relevant respects. For example, consider a principle of utility that requires a maximization of people's happiness and minimization of unhappiness. In a society with very limited resources, considerations of utility could give rise to a rule requiring that elderly people be allowed to "die when they can no longer contribute to economic production.... In a society of abundance, however, old people can easily be supported when they are no longer productive."[34] In such a society it would tend to maximize happiness if all people could be assured of support in their declining years.

While I agree with Macklin's conceptual approach, I must express reservations about her principle of humanity, particularly with her identification of "recognition of... the basic autonomy" of human beings as a criterion for the evaluation of a society's moral progress. Macklin and I agree that one leading candidate for what she calls "an ultimate moral principle" is the Kantian categorical imperative (also known as the principle of respect for persons): "So act as to treat humanity, whether in thine own person or in that of any other, in every case as an end withal, never as a means only." The key concept is that persons are never to be treated only or merely as means to another's ends. When one goes beyond this level of formality or abstraction, the principle begins to lose its universality. When this principle is elaborated to require, for example, that all persons are to be treated as self-determining, it loses its relevance to some cultures in which individual self-determination is less highly valued than it is in the United States.[35]

American universalists would argue that persons in such cultures must be educated; they must be taught to value self-determination as much as we do. Some might add that they must learn to value and protect the right to be self-determining or else

they will remain vulnerable to exploitation by those who have decision-making authority. Pluralists counter this argument by pointing out that the society seems functional as it is. If we impose on it our ethical standards, it may have a destructive effect on the culture. Furthermore, we should show respect for a society by allowing it to be self-determining.

In the specific context of research involving human subjects, there are some research and development activities that must be carried out in order to be responsive to the urgent health needs of persons who live in societies in which self-determination is not merely not highly valued: it is considered anti-social. There are, for example, certain tropical diseases that exist only or primarily in such societies. It seems inappropriate to say to persons in such societies that we will conduct research addressed to your health problems but only if you allow us to replace your ethical standards with our own. In my view, the conduct of such research in such populations with appropriate committee review, but with consent procedures that may fall short of the requirements of Western civilization, is responsive to the universally applicable requirement to refrain from using persons merely as means to the ends of others.

The *CIOMS Guidelines* reflect what I consider a satisfactory compromise position holding that some ethical standards are universal while recognizing the legitimacy of some degree of ethical pluralism. As noticed earlier, *CIOMS Guidelines* refer to universal principles as "transcending moral rules" without explicating what these rules are.

The recognition in *CIOMS Guidelines* that some moral principles are universal and that various cultures may develop very different rules to uphold the universal principles is implicit in their suggestion, referred to earlier, that the responsibility of ethical review committees in the external sponsoring country, "... may be limited to ensuring compliance with *broadly stated principles,* on the understanding that ethical committees in the host country *will have greater competence in reviewing the detailed plans for compliance in* view of their better understanding of the cultural and moral values." (emphasis added)

An inevitable feature of any document that aspires to global validity is that the fundamental principles must be stated at such

a level of abstraction that they do not seem to prescribe or proscribe very many behaviors. Further, such documents must necessarily have mostly procedural norms (which prescribe procedures for determining what actions are considered ethically acceptable in specific contexts) and relatively few substantive norms (which prescribe actions that must be performed in contexts that are defined, if at all, only in general terms).

ERRORS IN THE INTERNATIONAL DOCUMENTS

Nuremberg and *Helsinki* each contain statements that do not accurately reflect contemporary understandings of research ethics. In this section, examples of these errors and their unfortunate consequences are presented to those who have an interest in sponsoring, conducting, or reviewing research involving human subjects.

SITUATION IN TIME, PLACE, AND CONTEXT

A statement made by Fletcher and Schulman in their critique of U.S. federal policy is germane to our topic: " . . . if Federal policies on research with human subjects are understood as a moral code, it is necessary to keep their provisions under critical evaluation. Moral codes that cannot be tested and examined in the light of actual choices usually wither and die, because they lose relevance to ever new scientific questions."[36]

One important problem with the international documents is that they reflect the concerns and perspectives of the time in which they were written and of the individuals by whom they were written. I shall focus on *Nuremberg* to illustrate the nature of this problem.

Nuremberg was not addressed to the entire field of research involving human subjects as that field is currently understood. This document was written in response to the atrocities performed by Nazi physician-researchers during the Second World War. Its first principle--"The voluntary consent of the human subject is absolutely essential"--was and is clearly relevant for experiments of the sort that were assessed by the Nuremberg Tribunal. This principle is undoubtedly appropriate for research activities in which risk of physical or psychological injury is

presented to healthy, competent adults by procedures or interventions that do not hold out the prospect of direct benefit to the individual subjects. It is not appropriate, however, for randomized clinical trials of new, or old drugs involving children, for example. Moreover, it is not appropriate for research in the field of epidemiology involving no contact with individual humans apart from examining their medical records or computerized databases. Further, it is inappropriate for most research activities designed to evaluate innovations in programs or policies.[37]

In 1966, the United Nations General Assembly adopted the International Covenant on Civil and Political Rights of which article 7 states: "No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation." In context, it is clear that biomedical research was perceived in the 1960s as a type of torture or cruel, inhuman, or degrading treatment.[38] This is the same perspective that informed the drafting of *Nuremberg*. But this is not the way most thinking people envision biomedical research today.[39]

Most people who sponsor, conduct, or regulate research understand the historical origins and intentions of such statements in *Helsinki*, *Nuremberg*, and the International Covenant on Civil and Political Rights. As they perform in their professional roles, they apply such requirements only where such application is appropriate. However, serious problems are often created when naive persons get involved in the process. Among the adverse consequences of their involvement are occasional requirements by research ethics committees of extremely burdensome and unwarranted consent procedures for research involving record review or program evaluation. In some cases such naivete has resulted in unduly restrictive state or national regulation.[40]

Other types of problems may be caused by commentators who are not naive. I am referring to the *Nuremberg* fundamentalists, most of whom are academics who have credentials that appear to establish their credibility as experts in bioethics, who criticize ethically sound research programs or policies as being in violation of the *Nuremberg Code* or the International Covenant on Civil and Political Rights. Often such critiques compare the program or policy with the activities of Nazis because it is, after

all, the *Nuremberg Code* that is being violated.[41] Such criticisms are most typically found in newspapers and on television and occasionally in academic journals.[42] Such comments often cause a great deal of consternation on the part of lay readers and their representatives in legislative bodies.

CONCEPTUAL ERRORS

Problems are also created by conceptual errors in some of the international documents. One such error can be exemplified by placing one article of *Helsinki* developed for clinical research (II.6) in immediate proximity to one developed for nonclinical research (III.2).

> II.6. The physician 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.

These statements have several unfortunate and unintended consequences. First, many types of research cannot be defined as either clinical or nonclinical. Consider, for example, a placebo-controlled, clinical trial of a new drug. Certainly, the administration of a placebo for research purposes is not "justified by its potential diagnostic or therapeutic value for the patient." Therefore, according to *Helsinki*, this is nonclinical, and those who receive the placebo must be "either healthy persons or patients for whom the experimental design is not related to the patient's illness." This, of course, is unreasonable. Another unfortunate consequence is that a strict interpretation of *Helsinki* would lead us to the conclusion that all rational research designed to explore the pathogenesis or epidemiology of disease is to be forbidden. Because it cannot be justified as prescribed in article II.6, it must be considered nonclinical and therefore can be done only on healthy persons or patients not having the disease one wishes to investigate. This cannot be what those who drafted *Helsinki* intended.[43]

How could those who drafted *Helsinki* have made such errors? The most plausible explanation I can think of is that, as noticed earlier, the WMA, in creating the category they call clinical research, was concerned primarily with assuring the freedom of the physician "to use a new diagnostic or therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering" (*Helsinki*, article II.2). The class of activities contemplated under the rubric of clinical research in *Helsinki* is what has come to be called in the United States by such names as "compassionate use," "treatment use," "expanded access," and others. This class does not include controlled clinical trials.

Such errors as I have identified in *Helsinki* must be corrected. If we knowingly violate some of its standards routinely as, for example, when we design or conduct a placebo- controlled clinical trial, how can we insist that researchers comply with those of its other articles that are reasonable? The authority of the entire document is undermined if its errors are not corrected.

Helsinki, like *Nuremberg*, is also often cited inappropriately by commentators who may or may not be naive.[44] One recent example is the publication of a paper by Rothman and Michel which brands all or most placebo-controlled clinical trials unethical because they are in violation of *Helsinki*.[45]

Those who inappropriately appeal directly to *Nuremberg* or *Helsinki* as the ultimate source of ethical guidance have done a lot of damage by causing unnecessary confusion and consternation. Such damage could be limited if they appealed instead to the *CIOMS Guidelines* acknowledging the fact that the narrow focus of *Nuremberg* and the conceptual errors of *Helsinki* have been largely rectified by the *CIOMS Guidelines*.

RECOMMENDATIONS FOR FUTURE DEVELOPMENTS

I hope that I have presented sufficient evidence to persuade the reader that the *CIOMS Guidelines* represent a substantial improvement over their predecessors, *Nuremberg*, *Helsinki* and CIOMS's own *Proposed International Guidelines*. I am concerned that at this point it might seem to the reader that I believe that all

the problems associated with the development of international ethical guidelines for the conduct of biomedical research involving human subjects were identified and resolved by those who drafted the *CIOMS Guidelines*. I do not intend to leave the reader with this impression. More work remains to be done.

Like all ethical codes, the *CIOMS Guidelines* must be the object of constant critical evaluation. They must be revised from time to time in the light of actual experience and in response to problems that arise as they are applied to specific cases. If this is not done, then we may expect them to become outdated and irrelevant.

Some issues that must be considered and dealt with in future revisions of *CIOMS Guidelines* are anticipated in their background note: "Certain areas of research do not receive special mention in these guidelines: they include human genetic research, embryo and fetal research, and fetal tissue research. These . . . areas [are] in rapid evolution and in various respects controversial. . . . [Hence] it would be premature to try to cover them in the present guidelines."[46]

And, of course, there will be additional issues that we are now incapable of anticipating, just as in 1964 the authors of *Helsinki* could not anticipate the current dominance of the randomized clinical trial as the preeminent research strategy for validation of new therapeutic modalities, much less the intractable disputes that would subsequently be incited with the introduction of therapeutic fetal tissue transplantation.

I believe that there are some concepts in the *CIOMS Guidelines* that now, less than two years after their publication, should be reconsidered. For example, guideline 8 on research involving subjects in underdeveloped communities requires that "every effort will be made to secure the ethical imperative that the consent of individual subjects be informed." The only example provided in the commentary of a permissible exception to this rule is "when because of communication difficulties investigators cannot make prospective subjects sufficiently aware of the implications of participation to give adequately informed consent." Even in such cases the "investigator is required to ensure that each prospective subject is clearly told everything that would be conveyed if the study were to be conducted in a developed community."

In other words, it is necessary to thoroughly inform subjects even if there is nothing in their experience that could prepare them to grasp the meaning of, for example, Western concepts of disease causation. Subjects must invariably be informed "that they are free to refuse to participate . . . without loss of any entitlement." This rule is to be applied even in cultures in which departure from the course of action decided upon by the community is almost literally unthinkable. Such provisions in the *CIOMS Guidelines* suggest that this document continues to be excessively influenced by the legacy of *Nuremberg*.

The *CIOMS Guidelines* should also be revised to explicate the "transcending moral rules" to which they refer. The "general ethical principles" referred to in this document are not entirely satisfactory. For example, the version of the principle of respect for persons set forth in the *CIOMS Guidelines* is limited in its applicability by its focus on "respect for autonomy," a priority of Western civilization. As noticed earlier, respect for persons is a more universally valid principle when stated in terms of a prohibition of using human beings only or merely as means to another's ends.

Finally, for reasons I have argued elsewhere, I believe it would be very helpful to include cross-cultural anthropologists in the continuing process of evaluating, criticizing, and revising international ethical guidelines.[47] Other participants in the process of developing international guidelines, in their attempts at conducting dialogues across cultural boundaries, often inadvertently and unknowingly create confusion by relying on literal translations without awareness of the underlying symbolic and idiomatic meanings. This is why I believe we need the expert assistance of anthropologists in making our attempts at cross-cultural communication go beyond mere literal translation to the level of shared meanings.

NOTES

1. Parts of this paper are adapted or excerpted from the following three previous publications of the author: R.J. Levine, *Ethics and Regulation of Clinical Research*, 2nd ed. (Baltimore, Md.: Urban & Schwarzenberg, 1986); R.J. Levine, "Informed Consent: Some Challenges to the Universal Validity of the Western Model," *Law, Medicine & Health*

Care (1991): 207-213; R.J. Levine, "The International Dialogue on Health Policy, Ethics and Human Values: Recommendations for the Next Decade," *Poverty, Vulnerability, and the Value of Human Life: A Global Agenda for Bioethics. Proceedings of the 28th CIOMS Conference* (Geneva: CIOMS, 1994), 234-42.

The author was co-chair of the steering committee of the group that developed the CIOMS/WHO *International Ethical Guidelines for Biomedical Research Involving Human Subjects.*

2. CIOMS/WHO, *International Ethical Guidelines for Biomedical Research Involving Human Subjects.* (Geneva: CIOMS, 1993) The preface and guidelines of this booklet are printed in this book's Appendix F.

3. In this article the term "universal" refers to principles and guidelines that are thought to apply in all human societies and in all historical periods. Other terms such as "global" or "world-wide" refer to principles and guidelines that are thought to apply to all human societies but not in all historical periods. The authors of global guidelines expect them to require periodical revision.

4. N.A. Christakis and R.J. Levine, "Multinational Research," *Encyclopedia of Bioethics,* revised ed., (New York: Simon & Schuster Macmillan, 1995), 1780-87.

5. M. Grodin, "Historical Origins of the Nuremberg Code," in *The Nazi Doctors and the Nuremberg Code: Human Rights in Human Experimentation,* ed. G.J. Annas and M.A. Grodin (New York: Oxford University, 1992): 121-144, at 137.

6. As quoted in G.J. Annas and M.A. Grodin, eds., *The Nazi Doctors and the Nuremberg Code,* 104.

7. S. Perley *et al.*, "The Nuremberg Code: An International Overview," in *The Nazi Doctors and the Nuremberg Code,* 149-173, at 152.

8. T. Taylor, "Opening Statement of the Prosecution, December 9, 1946," in *The Nazi Doctors and the Nuremberg Code,* 67-93, at 67.

9. Grodin, "Historical Origins of the Nuremberg Code," 134-147.

10. A.R. Jonsen, "Do No Harm," *Annals of Internal Medicine* 88 (1978): 827-32.

11. Grodin, "Historical Origins of the Nuremberg Code," 124-32.

12. *Ibid.*, 126.

13. H. Wigodsky and S.K. Hoppe, "Humans as Research Subjects," in *Birth to Death: Biology, Science and Bioethics*, ed. D.C. Thomasma and T. Kushner (Cambridge: Cambridge University, 1995), in press.

14. Grodin, "Historical Origins of the Nuremberg Code," 134.

15. Perley *et al.*, "The Nuremberg Code: An International Overview."

16. *Ibid.*, 158.

17. *Ibid.*, 157.

18. I do not mean to imply that a requirement for informed consent is uniquely American. The philosophical basis of informed consent is more properly characterized as a product of Western civilization. Even American writers typically refer to Europeans as the source of the philosophical grounding for the informed consent requirement. However, the uniform requirement for informed consent to research and to medical practice developed earlier in the United States than in other nations. This, I believe, reflects the great emphasis placed on individualism and self-determination in the American social definition of the "person." See Levine, "Informed Consent: Some Challenges to the Universal Validity of the Western Model."

There is further cause for concern about imposing an American perspective on the development of international guidelines. As anthropologist Willy De Craemer has observed, in his summary statement on the American perspective:

> Taken as a whole, our [American] conception of personhood has at least one major paradoxical attribute. Although it places a high positive value on a universalistic definition of the worth, dignity, and equality of every individual person, it tends to be culturally particularistic, and inadvertently ethnocentric. To a significant degree, it rests on the implicit assumption that ideas about personhood are common to many, if not most, other societies and cultures. Beyond that, it assumes that the American way of thinking about the person represents the way men and women of all societies and cultures should and do think about personhood when they are being supremely rational and moral.

W. De Craemer, "A Cross-Cultural Perspective on Personhood," *Milbank Memorial Fund Quarterly-Health and Society* 61 (Winter 1983): 19-34.

19. Grodin, "Historical Origins of the Nuremberg Code, 136.

20. Levine, *Ethics and Regulation of Clinical Research,* 323.

21. H.K. Beecher, "Ethics and Clinical Research," *New England Journal of Medicine* 274 (1966): 1354-60.

22. It is overly simplistic to think that the publication of a single document had a direct cause and effect relationship on the work of Beecher and the USPHS Surgeon General. It is clear that Beecher was aware of the activities of the World Medical Association and was in communication with WMA before publication of *Helsinki* (Perley *et al.*, "The Nuremberg Code: An International Overview," 155). Also, those who were preparing the Surgeon General's memorandum were aware of

Beecher's activities. And yet I believe that awareness of the WMA project, which began in 1953, and anticipation of its effect had direct influences on both Beecher and the USPHS Surgeon General.

23. Physicians are accustomed to professional autonomy and to professional self-regulation. See R.C. Fox, *The Sociology of Medicine: A Participant Observer's View* (Englewood Cliffs, N.J.: Prentice Hall, 1989). The privilege of and responsibility for self-regulation were accorded to the medical profession by various national and state governments, because it was recognized that the profession had a monopoly on a large body of esoteric knowledge. Since persons outside the profession could not master this large body of knowledge, governments had no real alternative to allowing medical professionals to be self-regulating. In exchange for this authority, the medical profession was expected to use its esoteric knowledge exclusively for the benefit of society and its individual members.

In the 20th century, there has been an increasing recognition that not all of the physician's professional activities are grounded exclusively, or even primarily, in esoteric knowledge. In the context of research involving human subjects, this recognition has given rise to the participation of persons other than physicians in creating rules such as those requiring informed consent and equitable selection of subjects.

For the same reason, persons who are not physicians have been appointed to membership on research ethics committees to ensure that research is planned and conducted in compliance with the rules.

24. CIOMS/WHO, *International Ethical Guidelines for Biomedical Research Involving Human Subjects,* 6.

25. M. Angell, "Ethical Imperialism? Ethics in International Collaborative Clinical Research," *New England Journal of Medicine* 319 (1988): 1081-83.

26. N.A. Christakis, "Ethical Design of an AIDS Vaccine Trial in Africa," *Hastings Center Report* 18 (June/July, 1988): 31-37; N.A. Christakis, "Responding to a Pandemic: International Interests in AIDS Control," *Daedalus* 118 (1989): 113-14.

27. Levine, "Informed Consent: Some Challenges to the Universal Validity of the Western Model."

28. CIOMS/WHO, *Proposed International Guidelines for Biomedical Research Involving Human Subjects* (Geneva: CIOMS, 1982).

29. C.B. IJsselmuiden and R.R. Faden, "Research and Informed Consent in Africa--Another Look," *New England Journal of Medicine* 326 (1992): 830-34.

30. E. Ohnuki-Tierney, "*Illness and Culture in Contemporary Japan: An Anthropological View*" (Cambridge: Cambridge University Press, 1984).

31. R. Macklin, "Universality of the Nuremberg Code," in *The Nazi Doctors and the Nuremberg Code,* 240-76, at 242.

32. *Ibid.,* 242.

33. *Ibid.*

34. *Ibid.,* 244.

35. Levine, "Informed Consent: Some Challenges to the Universal Validity of the Western Model."

36. J.C. Fletcher and J.D. Schulman, "Fetal Research: The State of the Question," *Hastings Center Report* 15 (April 1985): 6-12.

37. J. Lynn, J. Johnson, and R.J. Levine, "The Ethical Conduct of Health Services Research: A Case Study of 55 Institutions," *Clinical Research* 42 (1994): 3-10.

38. The concept reflected in article 7 of the International Covenant on Civil and Political Rights was actually drafted at about the same time as *Nuremberg* as the Universal Declaration of Human Rights, which was adopted by the United Nations General Assembly in 1948.

39. R.J. Levine, "The Impact of HIV Infection on Society's Perception of Clinical Trials," *Kennedy Institute of Ethics Journal* 4 (1994): 93-98.

40. P. Riis, "The Danish Brain Collection and its Important Potentials for Future Research," *IRB: A Review of Human Subjects Research* 15 (November-December 1993): 5-6; C.G. Westrin, "Ethical, Legal and Political Problems Affecting Epidemiology in European Countries," *IRB: A Review of Human Subjects Research* 15 (May-June 1993): 6-8.

41. A.L. Caplan, "The Doctors' Trial and Analogies to the Holocaust in Contemporary Bioethical Debates," in *The Nazi Doctors and the Nuremberg Code,* 258-75.

42. R.J. Levine, "Commentary on E. Howe's and E. Martin's 'Treating the Troops,' " *Hastings Center Report* 21 (March-April 1991): 27-29.

43. Levine, *Ethics and Regulation of Clinical Research.*

44. There are *Helsinki* fundamentalists as well as *Nuremberg* fundamentalists.

45. K.J. Rothman and K.B. Michels, "The Continuing Unethical Use of Placebo Controls," *New England Journal of Medicine* 331 (1994): 394-98.

46. CIOMS/WHO, 1994: *International Ethical Guidelines for Biomedical Research Involving Human Subjects,* 7.

47. Levine, "The International Dialogue on the Health Policy, Ethics and Human Values."