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LECTURE

INTERNATIONAL CODES OF RESEARCH ETHICS: CURRENT CONTROVERSIES AND THE FUTURE*

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INTRODUCTION

In the past decade, 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 codes of ethics each has serious flaws that limit its applicability in low resource countries as well as in those that are wealthy.

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

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believe that most of the "novel" problems presented by AIDS have been there all along. There are social and political features of the AIDS pandemic that 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*[2] and the Council of International Organizations of Medical Science's *International Ethical Guidelines for Biomedical Research Involving Human Subjects*.[3] A full discussion of each of these documents and their relation to each other is beyond the scope of this Article.[4] 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.

I. THE *DECLARATION OF HELSINKI*

The *Declaration of Helsinki* was first promulgated by the World Medical Association (WMA) at its meeting in Helsinki, Finland in 1964; subsequently it has been amended several times.[5] I believe that the *Declaration* urgently requires revision.[6] 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 "non-therapeutic"; 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. Second, 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 established by the *Declaration*. This widespread and routine disregard for the *Declaration* undermines its authority and credibility.

Some commentators on the fifth edition of the *Declaration of Helsinki*

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1. *See* Robert J. Levine, *The Impact of HIV Infection on Society's Perception of Clinical Trials*, 4 KENNEDY INST. OF ETHICS J. 93, 93-98 (1994).

2. WORLD MEDICAL ASS'N, DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (1964) (amended 1975, 1983, 1989, 1996, & 2000), http://www.wma.net/e/policy/17c.pdf.

3. COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES, INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (1993).

4. For a more complete discussion of these documents, see Robert J. Levine, *International Codes and Guidelines for Research Ethics: A Critical Appraisal*, *in* THE ETHICS OF RESEARCH INVOLVING HUMAN SUBJECTS: FACING THE 21ST CENTURY 235-59 (H.Y. Vanderpool, ed. 1996).

5. *See* WORLD MEDICAL ASS'N, *supra* note 2; COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES, *supra* note 3.

6. *See* Robert J. Levine, *The Need to Revise the Declaration of Helsinki*, 341 NEW ENG. J. MED. 531, 531-34 (1999).

(*Helsinki V*) stated that some of its requirements—particularly with regard to the use of placebo controls in clinical trials—were misunderstood because they were unclear. According to such commentators, a major reason for revising the *Declaration* would be to clarify the meanings that were intended by the authors.

The *Declaration of Helsinki* has recently been revised extensively; the primary purposes of this revision were to address and resolve the aforementioned problems. The current version was promulgated by the WMA in Edinburgh, Scotland in October 2000.[7] In this Article, I will first consider the problems presented by *Helsinki V*.[8] Then I will consider the revisions embodied in the most recent, sixth edition (*Helsinki VI*), concentrating on those revisions that were designed to correct the problems I have identified. This appraisal leads to the conclusion that the revisions retain the errors of *Helsinki V*; *Helsinki*'s position on placebo controls is essentially unchanged and, while the revision removed the language of "therapeutic" and "non-therapeutic" research, the document still relies on this distinction and retains its associated errors.

II. THERAPEUTIC AND NON-THERAPEUTIC RESEARCH

First, let us consider the distinction between therapeutic and non-therapeutic research. Section II of the *Helsinki V* sets forth the guidelines developed for therapeutic research; Section III is concerned with non-therapeutic research. Putting one article from Section II in immediate proximity to 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 fields of pathogenesis, pathophysiology, and epidemiology. Consider, for example, a recently published study that examines the role of neurotransmitters in the pathogenesis of mental depression. This study was non-therapeutic. 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 non-therapeutic; when they are all

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7. See WORLD MEDICAL ASS'N, *supra* note 2.

8. *See id.* The fifth edition was promulgated by the WMA in Somerset West, Republic of South Africa in October 1996. *Id.*

non-therapeutic, use of the term "non-therapeutic research" might be justified. Every clinical trial has some components that are non-therapeutic. When we evaluate entire protocols as either therapeutic or non-therapeutic, 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 non-therapeutic 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 been frequent. In trials of thrombolytic therapy, repeated coronary angiograms have been performed on patients who had clinical indications for only one. Liver biopsies have been performed for no reason other than to disguise treatment assignments in a double-blind placebo-controlled trial. Repeated endoscopies have been performed in a population of patients with peptic ulcers who had clinical indications for no more than one. Placebos have been administered by way of a catheter inserted in the coronary artery. I do not want to be misunderstood as saying that any of these procedures were unethical. I am simply arguing that they should not be justified according to standards developed for "therapeutic research."

These examples illustrate the necessity of 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 non-therapeutic 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.[9] 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.[10] They are referred to in the regulations as either beneficial or non-beneficial. The justification of beneficial procedures is similar in principle to that employed in the practice of medicine. The intervention or procedure must hold out for the individual patient-subject the prospect of an improvement in his or her health. Moreover, in most cases there should be no other therapeutic procedure known to be superior to that of those 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.[11]

Obviously, non-therapeutic procedures cannot be justified in terms of their

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9. *See* Robert J. Levine, *Clarifying the Concepts of Research Ethics*, 9 HASTINGS CENTER REP., June 1979, at 21-26; *see also* ROBERT J. LEVINE, ETHICS AND REGULATION OF CLINICAL RESEARCH (2d ed. 1988) [hereinafter LEVINE, ETHICS AND REGULATION].

10. 45 C.F.R. § 46.405-406 (2001).

11. *See* 45 C.F.R. § 46.11(a)(2); LEVINE, ETHICS AND REGULATION, *supra* note 9.

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 non-beneficial procedures is limited by the so-called threshold standards in the regulations. For example, for research involving children, non-beneficial 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 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,"[12] and "[t]he intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in [the subjects'] actual or expected medical . . . situations."[13] Interventions or procedures that present more than a minor increase over minimal risk must be reviewed and approved at the national level.[14]

III. BEST PROVEN THERAPEUTIC METHOD STANDARD

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

> 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 one withholds 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 H_2 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 what I mean by embarrassing.

Article II.3 also forbids placebo controls in clinical trials in which there are virtually no risks 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 are very remote possibilities of adverse consequences of

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12. 45 C.F.R. § 46.406(c).
13. 45 C.F.R. § 46.406(b).
14. 45 C.F.R. § 46.407(b).

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 any 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. Incidentally, it is worth noticing that such publication is yet another routine violation of *Helsinki V*; 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 it 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 the field of research ethics since the 1970s. The debate began with an article in *The New England Journal of Medicine*, which 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.[15] The editor of the *New England Journal* opined that these trials were, in certain respects, reminiscent of the notorious Tuskegee Syphilis Studies;[16] 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," which asserts that the Western vision of research ethics must dominate the conduct of research everywhere in the world.

Let us consider these clinical trials in some detail as a case study. At the time the trial began, and indeed to this day, the standard in industrialized countries such as the United States is the so-called 076 regimen. The name comes from AIDS Clinical Trial Group (ACTG) protocol number 76 which established its safety and efficacy. The 076 regimen reduces perinatal transmission of HIV infection by about sixty-seven percent; the cost of the chemicals alone for treating each infected pregnant woman was about $800 in 1997. Why, one might ask, 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 eighty times the annual per capita health expenditure in many of the sub-Saharan African countries in which

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15. Peter Lurie & Sidney Wolfe, *Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries*, 337 NEW ENG. J. MED. 853, 853-56 (1997).

16. Marcia Angell, *The Ethics of Clinical Research in the Third World*, 337 NEW ENG. J. MED. 847, 847-49 (1997).

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.[17]

Provision of the 076 regimen would also have required a revision of the customs within the host countries for seeking perinatal care. In most of these countries, women 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, there are no facilities for the intravenous administration of anything. Finally, in the host countries for these trials, with the exception of Thailand, women breast feed their newborn babies even when they know they have HIV infection. The risk providing the babies with any available alternatives to breast feeding may be even greater than the risk of exposing them to HIV infection through breast feeding. The transmission rate of HIV infection by way of breast feeding is about fourteen percent. However, 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 four 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.

In summary, 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 foreseeable 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. Finding these methods 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 ten percent 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).[18] This document, which, unlike any other international document, explicitly addresses the

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17. For a more complete discussion of these problems, see Robert J. Levine, *The "Best Proven Therapeutic Method" Standard in Clinical Trials in Technologically Developing Countries*, 20 IRB: A REVIEW OF HUMAN SUBJECTS RESEARCH, Jan./Feb. 1998, at 5-9.

18. COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES, *supra* note 3.

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.[19] Second, it requires that any product developed in the course of such research must be made reasonably available to the inhabitants of the host country.[20] This, then, focuses multinational research on the needs of the country in which the research is carried out. These provisions are designed to put a stop to the practice by some corporations of conducting phase one drug studies in Africa simply because it is 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."[21] 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."[22] Also in regard to phase two and phase three 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 . . . ."[23]

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.[24] The relevant standard is the one that prevails in the host country.[25] I think it would be unethical to withhold anything that is generally available in the host country in order to do research designed to evaluate something else when such withholding could result in a non-trivial injury to the subject.

IV. 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.[26] 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

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19. *Id.*
20. *Id.*
21. *Id.*
22. *Id.* (Art. II.1).
23. *Id.*
24. *See* Levine, *supra* note 17.
25. *Id.*
26. *Id.*

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.

Those who insist that *Helsinki V* 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 proven therapeutic method (that is, 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 advantages 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.

V. THE REVISIONS IN *HELSINKI VI*

As mentioned earlier, one of the major reasons for the most recent revision of *Helsinki VI* was to clarify its position on the ethical justification of placebo

controls. I find no reason to believe that *Helsinki V* was either equivocal or susceptible to differing interpretations. Now let us consider whether *Helsinki VI* changes any aspect of its position on placebo controls. The relevant new passage is Article 29, the replacement for Article II.3 in *Helsinki V*:

> 29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.[27]

The only improvement over Article II.3 is the removal of the proscription of the development of all new therapies for conditions for which there are already existing "proven" therapies. And even this salutary effect is not entirely clear; it depends completely on the interpretation of the new Article 28. The *Declaration*'s absolute proscription remains intact for placebo controls in clinical trials designed to evaluate therapies for diseases or conditions for which there already exists a therapy known to be at least partially effective.

The other major reason for the revision of *Helsinki V* was to remove the spurious distinction between "therapeutic" and "non-therapeutic" research with all of its attendant problems. The WMA also failed in this regard. Although the language of "therapeutic" and "non-therapeutic" research has been removed from the document, the concept remains. There still is a section called "C. Additional Principles for Medical Research Combined with Medical Care."[28] The first article in this section is:

> 28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.[29]

As noted earlier, all research includes some components that are neither intended nor expected to be therapeutic. *Helsinki VI* persists in demanding that in "research combined with medical care," the entire protocol must be justified in terms of its potential prophylactic, diagnostic or therapeutic value.[30] The door to the fallacy of the package deal remains wide open.

VI. IMPACT OF THE *HELSINKI* REVISION

The *Declaration of Helsinki* has been violated routinely by medical researchers ever since it was first promulgated in 1964. Researchers who think about the requirements of *Helsinki* have noticed that their colleagues do research,

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27. WORLD MEDICAL ASS'N, *supra* note 2 (amended 2000).
28. *Id.* at 4.
29. *Id.*
30. *Id.*

for example, in the field of pathogenesis and use placebo controls in studies of new oral hypoglycemics. They have further noticed that these colleagues are not criticized as unethical. Rather, their research is rewarded by the traditional coins of the academic realm. The rewards include publication in respectable medical and scientific journals by editors who have proclaimed publicly their commitments to honor the *Declaration*. This includes its enjoinment against publication of reports of research conducted "not in accordance with [the *Declaration*'s] principles."[31] Recognition that some articles of *Helsinki* are both routinely violated and widely believed to be erroneous tends to undermine the credibility and authority of the entire document. Researchers who notice that virtually everyone violates Article III.2 of *Helsinki V* with impunity feel free to pick and choose among the other articles to see whether they wish to behave in accord with them.

The WMA deserves congratulations on the accomplishments reflected in *Helsinki VI*. Much language that was either faulty or archaic, or both, was replaced by more apposite wording. However, the two major flaws that provided the stimulus for this revision remain uncorrected: the distinction between therapeutic and non-therapeutic research and the excessively rigid proscription of placebo controls. I see no reason to suspect that the current iteration of these flawed articles in *Helsinki VI* will command any more respect than did their predecessors.

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31. *See* WORLD MEDICAL ASS'N, *supra* note 2 (*Helsinki V*, Art. 1.8; *Helsinki VI*, Art. 27).