On the 2008 Revisions to the WMA Declaration of Helsinki

JMAJ 52(5): 293–318, 2009

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Introduction

The primary objective of this paper is to provide point-by-point commentary on the Declaration of Helsinki (DoH) as revised at the General Assembly of the World Medical Association (WMA) in Seoul, South Korea in October 2008 while also reviewing those revision processes.

Work on these revisions was at the decision of the 176th WMA Council Session in Berlin in May 2007. The Council resolved to form a workgroup within the Medical Ethics Committee (MEC) to conduct a review of the 2000 DoH and work on revisions to it, and the workgroup was made up of representatives from the National Medical Associations (NMAs) of Brazil, Germany, Japan, South Africa, and Sweden. The two terms referred to the workgroup by the Council were (1) to draft new provisions for the noted paragraphs 29 and 30 that take account of those notes of clarification and to incorporate these into the main body of the declaration, and (2) to include in the main body of the declaration any matters that had arisen since 2000 requiring revision. The Council further set the Seoul General Assembly of October 2008 as the goal for adopting the revisions.

The members of the workgroup were Dr. J.L. Gomes do Amaral (Brazil), Dr. Ramin Parsa-Parsi (Germany), Dr. Masami Ishii (Japan), Dr. Kogsi Letlape (South Africa, former WMA president), Dr. Eva Nilsson Bågenholm (Sweden, group chair, and MEC chair), Professor John R. Williams (Canada, WMA ethics director), and Dr. Otmar Kloiber (WMA secretary-general). The author was permitted to attend meetings of the workgroup as legal adviser to the Japan Medical Association (JMA).

Prof. J.R. Williams took the lead in the group's work, himself originating drafts, coordinating the exchange of views among group members via email, and reworking draft revisions. In October 2007 the workgroup released a working draft, on which opinions were solicited from numerous stakeholders, including NMAs, WHO, the Council for International Organizations of Medical Sciences (CIOMS), and FDA. The workgroup then considered the received comments and prepared a draft revision in March 2008. At a symposium in Helsinki hosted by the Finnish Medical Association in March of that year, the workgroup heard views on the draft directly from such significant stakeholders as CIOMS and FDA. The views expressed there informed the group's draft of early April, which was submitted to the WMA Council Session in May. The deliberations of the Council and the MEC formed the basis of a new draft, which was opened for the NMAs and public comment. Meanwhile the WMA held symposia on the proposed revision in Cairo, Egypt and Sao Paulo, Brazil, with a second round of hearing of opinions from significant stakeholders. After the conclusion of the Sao Paulo conference co-hosted with the Associaçao Médica Brasileira, the full workgroup assembled to coordinate views on its final draft revisions. In early September the workgroup submitted its final version to the WMA Secretariat, and the Secretariat circulated these to the NMAs and made them publicly available.

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This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol.138, No.4, 2009, pages 752–769).

At the meeting of the MEC in October 2008, the final version was approved with a deletion of some words in the second sentence of paragraph 9 (the educationally, economically or medically disadvantaged), and the subsequent meeting of the Council approved the MEC draft unrevised. However, new paragraph 32, corresponding to the note of clarification to paragraph 29, and in particular that paragraph's second sentence met with sustained opposition from Brazil and South Africa, which sought the deletion of the second sentence, throughout the meetings of the MEC, the Council, and the General Assembly. Ultimately a sentence "Extreme care must be taken to avoid abuse of this option" was appended to the second sentence at the proposal of the American Medical Association (AMA) in the General Assembly and gained the approbation of three-quarters of those present in the Assembly but not the agreement of Brazil and South Africa. As a result, the draft including the AMA-proposed addition (substantively, the workgroup's final draft) was approved and adopted in the General Assembly.

The foregoing charts the progress of work on the 2008 revisions; the overall framework and text of the resulting 2008 DoH are much the same as those of the 2000 DoH. In this sense the 2008 DoH remains within the frame of the 2000 DoH. Quite rightly, care was taken with placement of its provisions, and the text was reworked to simplify and clarify the wording. On the other hand, in places new text was inserted reflecting the changes of the times. The result, therefore, might best be understood as going beyond small-scale revision and constituting medium-scale revision. The achievement of this outcome despite the short amount of time available for the work is due to the leadership of the workgroup demonstrated by Prof. Williams, who has devoted many years of work to the WMA ethics unit and become deeply familiar with past WMA declarations, and the rear support provided for his efforts by Secretary-General Dr. Kloiber, for which I would like to express once again my gratitude.

Of the principal issues demanding resolution in this round of revisions, the paragraph 29 issue concerning the use of placebos has its origin in the 2000 revisions, but the debate in fact started up long ago in the mid-1990s. Briefly, with the support of WHO, the U.S. government, and other parties, in the first half of the 1990s short-course AZT trials were conducted with placebo (no-treatment) controled groups in developing countries with the objective of preventing the mother-infant transmission of HIV, which was then epidemic in the developing world. A controversy arose within the U.S. claiming such research to be unethical in exploiting the difference in medical standards between developed and developing countries and treating the people of developing countries adversely (by way of selecting a no-treatment course that would not have been sanctioned in developed countries), and thus relationship between the rights and wrongs of a double standard in medical ethics and the DoH emerged as an issue.

This paper will therefore digress somewhat to discuss first how the 2000 DoH revisions took form and then outline the sharp external criticisms of the 2000 DoH and the WMA responses to those criticisms. An appreciation of this background should make the significance of the 2008 revisions yet clearer and also show us what direction the DoH ought to take in future.

The 2000 Amendment of the DoH

The AMA's draft revisions

Work on the DoH amendments adopted by the Edinburgh General Assembly in 2000 began with the submission of DoH draft revisions by the AMA to the 147th WMA Council Session in Paris in May 1997 with the request that they be adopted by the Hamburg General Assembly in November of that year. The background comment accompanying the draft revisions stated, "Central to this draft revision is the current belief on the part of many prominent research investigators and ethicists that, from an ethical perspective, there is no distinction between medical research combined with professional care (clinical research) and non-therapeutic biomedical research involving human subjects (non-clinical biomedical research). Although this appears to be a major shift in emphasis for the Declaration, making this change allows a consistency of focus and presentation that was not previously possible." Consisting of two chapters titled Introduction and Basic Principles, the proposed draft would constitute sweeping change to the content and composition of the 1996 DoH, as in its abolition of the distinction between clinical and

non-clinical research. Although its authorship is uncertain, the text does strongly reflect the thinking of Yale University Prof. Dr. Robert J. Levine,*[2] who later participated in the DoH revision workgroup.

The AMA draft revisions (below, "the AMA draft") consisted of a nine-sentence Introduction and a five-section Basic Principles of 28 paragraphs [Fundamental Requirements for Conduct of Biomedical Research Involving Human Subjects (eleven paragraphs); Scientific and Ethical Review of Research Protocols (two paragraphs); Informed Consent and Selection of Research Subjects (eight paragraphs); Responsibilities of Physicians and Other Research Investigators (four paragraphs); and Data Management and Publication of Results(three paragraphs)]. The AMA draft increased the number of paragraphs in the 1996 DoH and made the text of individual paragraphs longer. Although this draft did not in the end become an official WMA proposal, it did influence subsequent work on DoH revision in a variety of ways.

The sense of the eighth sentence of the Introduction, for example—"It is important that the Declaration, and the principles enunciated in it, be considered and applied in its entirety to avoid misunderstanding and misinterpretation that could result from taking a section out of context."—is incorporated into the 2008 amendments as the second sentence of paragraph 1.

Nor may the proposals in the Basic Principles of paragraph 8 Clinical care for research subjects—"In any research study that involves subjects with an ongoing need for clinical care, it is particularly important that all research subjects, including those in a control group, if any, be provided with **appropriate** diagnostic, therapeutic, and prophylactic interventions for aspects of their care not related directly to the research intervention for which they have given consent"—and paragraph 9 Randomization of subjects and use of placebo—"The principle of assuring appropriate diagnostic and therapeutic care for research subjects does not exclude the use of randomization of the subjects to defined treatment groups in the protocol, including the use of placebo or, for defined periods of time, providing placebo or no treatment if justified by a scientifically and ethically sound research Protocol."—be neglected as the provisions that were the origins of the paragraphs 29 and 30 debates in 2000.

The former of these paragraphs corresponds to the first sentence—"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."—of paragraph II3 of the 1996 DoH, and the latter to its second sentence—"This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists." However, a close comparison of the language makes it clear that, in revising "the best proven" in the first sentence of the 1996 DoH to "appropriate" in paragraph 8 of the AMA draft and "where no proven diagnostic and therapeutic methods" in the second sentence to "if justified by a scientifically and ethically sound research protocol" in paragraph 9, in each of these instances the AMA draft sought to relax the restrictions of the 1996 DoH extensively.

Reactions to the AMA draft

In early 1998 the AMA draft was circulated to the NMAs for their comments. NMA reactions to the AMA draft divided cleanly in two. Japan and such European countries as the United Kingdom, Germany, France, Spain, and Sweden recognized the need to make minor revisions to the 1996 DoH, but expressed strong objections to abolishing the distinction between clinical and non-clinical research and to sweeping changes to the framework, form, and content of the existing declaration. On the other hand, members including Canada and Israel expressed their basic approval of the AMA draft.*[3]

In an opinion drafted for the German Medical Association, Göttingen University professor of law Erwin Deutsch stated, "The continental European states have for a long time recognized the basic difference between purely scientific investigations and therapeutical trials. The French statute of 1988 is based on that notion and even the responsibilities established in that statute are different: For purely scientific research there is strict liability, for research with benefit for the subject there is liability because of presumed fault. In other countries the differentiation between purely scientific and therapeutical research is recognized too: For instance in Germany by the famous case BGHZ, 20, 61 (Thorotrast at the Heidelberg University Clinic). Ethics committees routinely base their deliberations on this difference. The German Pharmaceutical Act

§§40 et sq. is based on the differentiation of the two forms of research. Even the European Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, art. 17 uses the difference between the two types of investigation."[1]

Appleyard workgroup and its draft revisions

In view of the opposition of several NMAs, the 150th WMA Council Session in Montevideo, Uruguay, in April 1998 withdrew the AMA draft and began afresh. The WMA additionally formed a workgroup within the MEC to study the question of DoH revision independently and appointed representatives as members of the workgroup: Dr. James Appleyard (UK, group chair, and MEC chair), Dr. Nancy Dickey (AMA president), Dr. Masamichi Sakanoue (JMA advisor), and Prof. J.R. Williams (Canadian Medical Association ethics officer). At the recommendation of the AMA, the WMA also requested the aforementioned Prof. R.J. Levine to participate as coordinator and facilitator.

There was considerable divergence in the thinking of the individual workgroup members, however, and the work of revision did not always go smoothly. After many twists and turns, Prof. Levine in December 1998 prepared a first draft and, having coordinated views within the workgroup, presented the WMA with the finalized draft revisions (below, "the Levine draft") in March 1999. WMA Secretary-General Dr. Delon Human (South Africa) gave this draft the title "Proposed Revision of the World Medical Association Declaration of Helsinki (Doc. 17. C)" and circulated it to the NMAs for their comments, also releasing the document to the public.

Running to 34 paragraphs (or articles) in all, the Levine draft stated in its Introduction that the emergence in the 1960s and thereafter of "randomized clinical trial" to verify the effectiveness and safety of treatments and the resultant of composite research comprising both clinical and non-clinical elements had now rendered irrelevant the distinction between clinical and non-clinical research, and committed to the statement (Introduction, paragraph 8), "For this reason, the distinction is no longer used in this Declaration."

In all, the text was made up of sections titled Introduction (twelve paragraphs), Fundamental Requirements for Conduct of Biomedical Research Involving Human Subjects (seven paragraphs), Scientific and Ethical Review of Research Protocols (two paragraphs), Informed Consent and Selection of Research Subjects (seven paragraphs), Responsibilities of Physicians and Other Investigators (three paragraphs), and Data Management and Publication of Results (three paragraphs). As a comparison of the Levine draft and the AMA draft shows, it differed little from the AMA draft in either form or content.

Criticism of the Levine draft

The debate over whether the Levine draft would be proclaimed or no was one literally global and international.

On line of criticism was the disagreement voiced in the *New England Journal of Medicine* (*NEJM*) in 1997 by Peter Lurie and Sidney M. Wolfe of the consumer group Public Citizen criticizing the randomized placebo- (no-treatment)-controlled trials of short-course AZT with which Levine had been involved.[2] In addition the two wrote jointly to the WMA secretary-general a scathing letter of 29 March, 1999. Troyan A. Brennan also contributed a critical article to the *NEJM*. In substance, its thinking appears to be identical to Public Citizen's. They criticized the Levine draft for a runaway rationalism that discriminated against research subjects in developing countries by accepting local rules (or a double standard), scrutinized the growing scope of placebo use, and accused the draft of markedly impairing the ethos of protection of subjects that is the foundation of the DoH.[3]

Another was criticism voiced principally by Continental medical law scholars. Many countries in the tradition of Continental law have a history of differentiating the legal responsibilities of researchers with respect to subjects harmed in research by distinguishing between clinical and non-clinical research. As the Levine draft renounced this distinction in one swoop, it could be difficult for Continental medical law scholars to accept the draft. Representative of this perspective is the view of Prof. Dr. E. Deutsch, quoted above in connection with the AMA draft, as stated in the 20-point "Göttingen paper"*[4] outlining the outcome of discussion at the international symposium "Forschungsfreiheit und Forschungskontrolle in der Medizin —zur geplanten Revision der Deklaration von Helsinki" (Freedom of research and control of

research in medicine: The planned revision of the Declaration of Helsinki) held at Göttingen University in 1999.

On top of the divergent thinking of the U.S., which sought the abolition of the distinction between clinical and non-clinical research, and Europe and Japan, which on the contrary the distinction best maintained, was a confrontation between developed countries (the U.S. in particular) and developing countries (Brazil and South Africa in particular, and the Public Citizen which supported them) that criticized the conduct of randomized placebo (no-treatment) controlled trials in developing countries under conditions disadvantageous relative to those of subjects in developed countries and the disproportionate enjoyment of the results, when the Levine draft was tabled, markedly exacerbated the discussions themselves. The outcome was the failure of the product of the 1999 workgroup with its Anglo-American core and in which the JMA also participated. Perhaps due to the language barrier, the repeated contention of the JMA to the workgroup that the 1975 DoH need not be modified in form or language but only made more "concise" was not duly heeded.

Significant proposals of the Levine draft

The Levine draft contains throughout significant proposals not found in previous versions of the DoH. Examples are paragraph 16 Altruistic participation in research, paragraph 18 Access to health care, paragraph 19 Controlled clinical trials, paragraph 26 Research involving women, and paragraph 27 Research involving vulnerable subjects.

For reference in the discussion to follow, here I will reproduce the text of paragraphs 18 and 19 concerning randomized placebo-controlled trials.

> §18 Access to health care: In any biomedical research protocol every patient-subject, including those of a control group, if any, should be assured that he or she will not be denied access to the best proven diagnostic, prophylactic or therapeutic method that would otherwise be available to him or her. This principle does not exclude the use of placebo or no-treatment control groups **if such are justified by a scientifically and ethically sound research protocol**.
>
> §19 Controlled clinical trials: The central ethical and scientific justification for conducting a controlled clinical trial in which the outcome measures are either death or disability is that there is within the expert clinical community genuine uncertainty or otherwise irreconcilable controversy as to which of the two or more interventions or procedures to be compared is superior. This justification criterion applies equally to clinical trials in which the control group will receive placebo or no active treatment. When outcome measures are neither death nor disability, placebo or other no-treatment controls may be justified on the basis of their efficiency.

While formally restricting randomized placebo (including no-treatment) controlled research (trials) to some degree, these two paragraphs in fact admit it to a prodigious extent. Although the wording is somewhat different, the purport of their content is the same as the 1997 AMA draft and is a broad relaxation of restrictions on randomized placebo-controlled research.

Setting aside the issue of conducting research (trials) overseas, one observes leniency in the domestic American standards for conducting randomized placebo-controlled research and in their practice. The issue that in reality arose was the attempt to apply these domestic standards uniformly in developing countries where the healthcare environment was different.

Dickey workgroup

At the meeting of the MEC in Santiago, Chile in April 1999, near to half of the committee was in opposition to the Levine draft, and seeing no way to build consensus within the committee, the workgroup withdrew the proposed draft. As a compromise the MEC established a new workgroup, with several conditions attached,[*5] made up of three women—Dr. Nancy Dickey (group chair, AMA president), Dr. Judith Kazimirski (Canadian Medical Association), and Dr. Kati Killymäki (Finnish Medical Association)—and resolved to continue the work on revision further, and the Council approved this course.

This workgroup held its first meeting in Ottawa in August 1999 and then worked vigorously on revision through to the autumn of 2000. In May 2000 the workgroup presented its 1st draft revisions to the 156th Council Session in Divonne-les-Bains, then prepared its 2nd version with the Council's input, followed by its 3rd version based on internal consensus, which it circulated to NMAs and outside stakeholders for comment.

The 2000 draft revisions

In September the workgroup prepared its 4th draft revisions, which it submitted to the MEC in 2000 and also made publicly available. The 4th version was made up of these chapters: A. Introduction (nine paragraphs), B. Basic Principles for All Medical Research (seventeen paragraphs), and C. Additional Principles for Medical Research Combined with Medical Care (five paragraphs).

In their abolition of the distinction between clinical and non-clinical research, the 4th version draw near the 1997 AMA draft and 1999 Levine draft. In trimming as close as possible to the current DoH, however, and in particular in their wording and structure, they exhibited a regard for European and other objections. The question was how they responded to the debate over randomized placebo (no-treatment) controlled research (trials). Paragraphs 24b and 23 in this connection were as given below. The following 4th version distributed to committee members marked insertions and deletions, denoting where it differed from the 3rd version distributed to the NMAs just before then. According to the text, both the deletions and the boldface are revisions made immediately prior to the General Assembly; they provide graphic indication of how the paragraph II3 of the 1996 DoH and the new paragraph 24b were qualitatively modified. Specifically, while paragraph 24b of the 3rd version appears at first glance identical to paragraph II3 of the 1996 DoH, the change of "best proven" to "proven effective" shows that in substance it is nearer to the Levine draft. (Meanwhile, paragraph 23 corresponds to paragraph II2 and is no different in content from the previous text.)

> §24b In ~~any~~ medical **research** ~~study,~~ **particularly that comparing currently accepted best proven methods against new methods**, every patient (including those of a control group, if any)—should be assured of **access to the best proven** ~~effective~~ prophylactic, diagnostic, and therapeutic methods **at the conclusion of study**. ~~24c.~~ This does not exclude the use of inert placebo in studies where no proven **prophylactic**, diagnostic or therapeutic methods exists.
>
> §23 The potential benefits, risks and discomfort of a new method should be weighed against **those** ~~the advantages~~ of the best current prophylactic, diagnostic and therapeutic methods.

Adoption of the 2000 amendments

The Edinburgh General Assembly in October 2000 discussed and debated the 4th version heatedly throughout, in meetings of the MEC, of the Council, and of the General Assembly. Ultimately debate focused on two questions: how to word the placebo provisions and post-study protection of the interests of research participants.*6 The debate went repeatedly with no room for compromise on the part of South Africa, Brazil, and others opposed, and a final decision was deferred to the MEC, reconvening on the evening prior to the General Assembly. Once again the participants served up the same arguments, and the issue remained unresolved past 11:30 p.m. The participants then took a break and commissioned the workgroup to prepare a final draft based on the discussion to that point. Reconvening near midnight, well past the scheduled time, the committee brought things to an extraordinary close in dim lighting with the unanimous approval by all the present of its 8th version, presented in PowerPoint and with no time to scrutinize the text adequately.

Thus did the 2000 DoH address not only the paragraph 29 issue concerning the use of placebos, which had been the main point of contention, but also produced an unexpected by-product in the form of paragraph 30 guaranteeing post-study research participants access to the best treatment.

Criticism of the 2000 DoH and the WMA's Response

Objections to the 2000 DoH

The 2000 DoH was met in early 2001 with a chorus of claims lodged by pharmaceutical firms and research organizations and bodies, first in the U.S. and then in the European Union, that the presence of paragraphs 29 and 30 made it unworkable as the domestic and international standard. The FDA, for example, made a point of issuing a "March 2001 Guidance to Industry"*7 in which it noted that FDA regulations referenced the 1989 Tokyo DoH*8 and made clear that it would not utilize later revised versions of the DoH.

This move by the U.S. government gave rise to the circumstance of the 2000 DoH being practically unused around the world. A major factor in the background to this development was the

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agreement by the U.S., the European Union, and Japan in May 1996 to the tripartite ICH-GCP and the inclusion in the ICH-GCP of a provision committing to compliance with the WMA's DoH (the 1989 version then extant). This is because the national governments involved thereby made DoH compliance obligatory.*[9–11]

Issues arising from the 2000 DoH

To provide an understanding of what issues arose, this discussion addresses the following two points of contention.

(1) Paragraph 29 (see left-hand column in page 310 below)

In paragraph 29 it is the wording of its second sentence endorsing placebo use and no-treatment courses that became an issue. It is the U.S. where placebo use and the debate are most advanced. In response to these arguments, the FDA has a history of approving a broad range of randomized placebo-controlled or no-treatment research (trials), and even recommending these methods, while also establishing restrictions on them. From this perspective, it is too narrow to limit placebo use and no-treatment courses to "where no proven treatment exists."

(2) Paragraph 30 (see left-hand column in page 311 below)

Paragraph 30 guarantees access to the best proven treatments to all participants in a study after the conclusion of the study. This is an extremely abstract prescription, and the author does not consider any concrete legal rights or obligations to arise directly from it in the relationship between researchers and subjects or research participants. (See note 11.) However, more than a few Western thinkers do consider it to give rise to rights and obligations or fear that it may do so. From their perspective, to guarantee the best treatments post-study is a problem that one cannot readily accept.

The various criticisms stirred up in various locales in response to the FDA criticism of the DoH in March 2001 ultimately focused on these two points of contention.

WMA response

Perceiving the situation to be a serious one, the WMA Council immediately entered on discussions of how to proceed. The proposal that emerged was to append a note of clarification to paragraph 29 at the 2002 Washington, D.C. General Assembly and one to paragraph 30 at the 2004 Tokyo General Assembly, each of which was approved and adopted by resolution of the General Assembly.

Although a note, the insertion of such 2002 wording does affect the sense of the original text. Oddly enough, the resolution met with no objection as such.

As is apparent from reading the notes of clarification to paragraphs 29 and 30, the note of paragraph 29 somewhat transforms its content and that of paragraph 30 completely eviscerates its effective content. The latter clearly exceeds the bounds of interpretation, and it would seem to have been preferable, if going so far, to modify the text itself. However, the WMA executive at the time sought to avoid reigniting the North-South confrontation with a clean swoop and instead cool things down over time, and so chose the path of leaping to the next stage while forming a consensus.

The WMA Council Session in May 2007 first formally announced a review of the 2000 DoH and consideration of revisions to it. A workgroup was immediately formed, which spent the subsequent 18-plus months working on draft revisions, as described above in section "Introduction."

The 2008 Amendments

2004 Version	2008 Version
Subtitle: Ethical Principles for Medical Research Involving Human Subjects **A. INTRODUCTION**	**Subtitle: Ethical Principles for Medical Research Involving Human Subjects** **A. INTRODUCTION**

Commentary: Whereas the 2004 chapter A had nine paragraphs, the 2008 chapter A has ten. This is because old paragraph 1 was broken into two paragraphs. Retaining unmodified the thought behind the 1975 Tokyo revision, the old paragraph 1 included persons other than physicians among those to whom the DoH applies. Some medical associations were steadfastly opposed to this and asserted that as the declaration of a society of physicians, its coverage should be limited to physicians.*[12] The 2008 revisions adopt this view, and new paragraph 1 limits the coverage of the declaration to physicians. Meanwhile, new paragraph 2 is a new construction recommending that persons other than physicians adopt the DoH principles.

Further, the insertion of the second sentence in the new paragraph 1 specifying a standard of interpretation for the provisions of the DoH and the insertion in new paragraph 5, corresponding to old paragraph 4, of the second sentence ("Populations that are underrepresented in medical research should be provided appropriate access to participation in research.") are new departures made during the 2008 revisions of chapter A. Although the wording is changed here and there in individual paragraphs, these do not go beyond rhetorical changes made for the purposes of clarity and simplicity.

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.	**1.** The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs. **2.** Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

Commentary: The old paragraph 1 is divided in the new paragraph 1 covering physicians and the new paragraph 2 covering non-physicians. In the old paragraph 1 those addressed by the declaration included non-physicians as well as, of course, physicians. In view of the fact that the DoH is a declaration of a society of physicians, however, its coverage in the new paragraph 1 is limited to physicians and meanwhile the new paragraph 2 introduced recommending adoption of the declaration by non-physicians. While the author considers the 2004 version unproblematic, the revised text reflects the strong view of European countries that, as with the change in 2000 from "biomedical research" to "medical research," the coverage and content of the declaration should be as distilled as possible.*[12]

Further, as noted at the outset, a second sentence is specifically inserted in the new paragraph 1 stipulating that the several provisions of the DoH should be interpreted as a whole. This insertion is due to the increase in recent years of persons who interpret individual provisions in isolation from the whole without taking into account why the DoH was drafted in the first place and the resultant confusion arisen in various locales.*[13]

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.	**3.** It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

Commentary: This paragraph is substantively the same as the old paragraph 2. Whereas the old paragraph 2 describes

a general duty to the patients of a physician, new paragraph 3 also touches on relationship with physicians and research, which is the main subject of the DoH.

3. 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."	**4.** The Declaration of Geneva of the WMA 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 in the patient's best interest when providing medical care."

Commentary: Like old paragraph 3, new paragraph 4 quotes the essence of the Declaration of Geneva and the International Code of Medical Ethics, the most important documents of the WMA. These documents, the former in particular, are termed the modern Hippocratic Oath, and in many developed countries of the West it is obligatory for a licensed physician joining a professional medical association to swear an oath substantively incorporating the Declaration of Geneva. Some Japanese healthcare personnel are not even aware of the existence and significance of these documents. Where physicians are engaged in medical research, however, it is necessary for those researchers to recognize and reaffirm their international obligations stated in the new paragraph 4 of the DoH that "The health of my patient will be my first consideration" and to "act in the patient's best interest when providing medical care."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.	**5.** Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

Commentary: Although the wording of the first sentence of new paragraph 5 is partially modified, it is substantively much the same as old paragraph 4.

Like the related new paragraph 17 of chapter B below, the inserted second sentence is entirely new content, and its implementation will need to be tracked carefully in countries overseas. As readers will be aware, participation in research has been denied or refused to, for example, children and women, and pregnant women in particular, on grounds of assuring and protecting their safety. The result has been that these populations have been unable to enjoy the fruits of up-to-date healthcare in some locales. The inserted second sentence is described by its original drafter as guaranteeing opportunities to participate in research to these populations also. Since these populations include large numbers of "vulnerable" people, however, researchers must exercise greater discretion in acting on it.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.	**6.** In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

Commentary: The wording of old paragraph 5 prioritizing the welfare of research subjects is modified somewhat, but substantively the same.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.	**7.** The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

Commentary: The first and second sentences of new paragraph 7 give order and simplicity to the text of old paragraph 6, with essentially the same substance. The new term "interventions" is used to cover the whole of "methods, procedures and treatments."

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.	**8.** In medical practice and in medical research, most interventions involve risks and burdens.

Commentary: A new paragraph 8 is a simplification of old paragraph 7, with no substantive change.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.	**9.** Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

Commentary: A new paragraph 9 is the result of deletion from old paragraph 8 of the phrases "those who will not benefit personally from the research" and "those who may be subject to giving consent under duress," and simplification of the text as a whole. The former of the deletions is premised on research subjects necessarily benefiting from research, and this was criticized as impossible. The second deletion is explained by the drafter as including them in the third sentence.

9. Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.	**10.** Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

Commentary: A new paragraph 10 is essentially the same as old paragraph 9. The text urges physician researchers to take into consideration national and international law and ethics, and cautions them against the laws and other regulations reducing or eliminating the protections of subjects. This is a strong statement of the WMA's will directed at governmental authorities in countries throughout the world.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH	**B. PRINCIPLES FOR ALL MEDICAL RESEARCH**

Commentary: Whereas the 2004 chapter B was made up of eighteen paragraphs, the 2008 chapter B is made up of twenty paragraphs, an increase of two. Its title has been revised from "Basic principles for all medical research" to "Principles for all medical research." However, it is important that the principles applied to all medical research on human beings in chapter B, whether clinical or non-clinical, are collective and comprehensive. This chapter is the core, so to speak, of the DoH. On the other hand, its content is not necessarily arranged in textbook-like fashion, and it combines principles different in kind.

The first of the principles stated is that physicians and researchers shall respect the life, dignity, integrity, and inviolability of research subjects and patients, and recognize their responsibility to protect their privacy. (new paragraphs 11, 16, and 23)

The second is, when conducting research on human subjects, the principle of undergoing prior evaluation of the design

and performance by a third party. Required are the creation of a protocol (research plan) to be evaluated, its examination and approval by an independent research ethics committee, and interim reporting on the research. (new paragraphs 14 and 15)

The third is dispassionate evaluation of the risks and benefits posed to patients and subjects involved in research and not to permit research unless the benefits to subjects are prioritized, including the adequate management of risks and the enjoyment of benefits of its results. (new paragraphs 17, 18, 20, and 21)

The fourth is the principle of the consent of the subjects themselves participating in research. The significant concern here is "informed consent" procedures. (new paragraphs 22 and 24–29) This is the most important part of the DoH that links it to the Nuremberg Code, and the provisions are more substantial than 2004 version. What is new among the 2008 revisions in this connection includes the registration of clinical trials (new paragraph 19), the incorporation into the new paragraph 15 of the note of clarification to the paragraph 30, and provisions for treating and/or compensating subjects who are harmed in trials. (new paragraph 14)

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.	**11.** It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

Commentary: In addition to "the life, health, privacy, and dignity" in old paragraph 10, new paragraph 11 consolidates important duties of physicians and researchers with respect to research subjects and patients, including protection of their "integrity," the "confidentiality of personal information" (new paragraph 21), and "self-determination."

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.	**12.** Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

Commentary: Partially revising old paragraph 11, which stipulated experimentation in the sequence of literature review, laboratory work, animal experiments, healthy human subjects, and patients, new paragraph 12 combines with these mention of the welfare of experimental animals that appeared in the latter half of old paragraph 12, with no substantive change. The rapid progress of scientific technique that has embraced medicine in recent years is naturally beginning to affect experimental and research procedures. In this sense, it must be recognized that the sequence stated in this paragraph is not necessarily absolute.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.	**13.** Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

Commentary: A new paragraph 13 stipulating concern for the environment is the same as the first half of the old paragraph 12. The second half has been moved to the end of the new paragraph 12.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in	**14.** The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and

conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

Commentary: New paragraphs 14 and 15 are reorganizations of old paragraphs 13 and 14. The new paragraph 14 governs "research protocols," and the new paragraph 15, as detailed below, the composition and work of "research ethics committees" (termed "ethical review committees" in the 2004 version).

The research protocols stipulated in the new paragraph 14 must include information on funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects, and provisions for treating and/or compensating subjects harmed as a consequence of participation in the research study. Also added to the end of this paragraph, reworked, are the old paragraph 30 guaranteeing post-study access to the best treatment and the note of clarification to paragraph 30 that was a de facto revision of it.

Of the information required in a research protocol, "conflicts of interest" had already been inserted at the time of the 2000 revisions. Together with the newly inserted provision for treatment and compensation for harm incurred by subjects, this urges the implementation of domestic law for the protection of research subjects. Unflagging attention is required for response and act on these issues in developed countries, particularly the EU countries.

According to the note of clarification to paragraph 30, "it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic methods identified as beneficial in the study," and post-trial access arrangements must be specified in the research protocol, which must be examined and reviewed by an ethical review committee. In the 2008 revisions, this note has been moved more or less intact to the end of the new paragraph 14. Substantively, it requires the prior inclusion of information regarding the research in the research protocol and also relies on the judgment of a research ethics committee. The note added complex procedures not contained in the 2000 DoH, and it is no exaggeration to say that at this stage the old paragraph 30 was completely eviscerated. Be that as it may, in order to guarantee that subsequent to research the participants will enjoy the benefits of its results, it required that these arrangements be detailed in the research protocol beforehand and submitted for review to a research ethics committee, and the 2008 revisions have brought the effectiveness of the noted paragraph 30 increasingly into doubt.

The work that the WMA Council charged the workgroup with was the incorporation of the notes to paragraphs 29 and 30 into the main body of the text, and even if revisions such as these were unavoidable, the author rather considers that deleting this wording would have left fewer issues to address in future.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made

	without consideration and approval by the committee.

Commentary: A new paragraph 15 introduces the term "research ethics committee" in place of "ethical review committee" as used heretofore and defines its composition, work, and role. At the time of the 2000 revisions, the committee had already been granted authority to monitor research; the 2008 revisions go a step further, the provisions that draw our attention being the obligation of researchers to provide monitoring information, and information about serious adverse events in particular, to the committee and the prohibition of changes to a research protocol without consideration and approval by the committee. A tendency is apparent for the mandate of the research ethics committee to grow with each revision, but is this really a good thing? A problem as important as this one should be dealt with by a basic rule in the declaration, and giving unconditional authority to the committee avoided to the extent possible. The reason is that encumbering the committee with responsibilities and duties beyond those necessary may well lead to rejection of the committees.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.	**16.** Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

Commentary: A new paragraph 16 stipulating the qualifications and responsibilities of research personnel maintains more or less intact the thinking behind old paragraph 15. The change in wording is in line with limitation of coverage of the declaration to physicians.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.	**17.** Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

Commentary: When an old paragraph 19 was first introduced in 2000, Prof. Dr. Jochen Taupitz commented thus:

> No.19 is completely new. However, the meaning of this stipulation is unclear, because it is not explained which criteria are to be used to differentiate "populations" from one another (age, disease etc. in the sense of nos. 24 and 26?). Obviously it is intended to solve one part of the problem of "ethical export," and the problem of conducting research in developing countries in particular, namely to prevent "research on the poor for the rich."[4]

The old paragraph 19 is a point of importance, established to prevent developed countries from exploiting the people of developing countries through research spanning multiple countries, especially research spanning developed and developing countries.

The 2008 revisions add the phrase "a disadvantaged or vulnerable population or community" to the front of the old paragraph 19, and go on the make slight changes to the subsequent text and relocate it.

The intention of the old paragraph 19 was to cover all medical research, but new paragraph 17 narrows the scope of the medical research dealt with. In this sense, we may call it a new provision that was not formerly present. The author of the draft explains this limitation as adding the phrase "disadvantaged population or community" to enable phase 1 trials on diseases (e.g. malaria) primarily impacting developing countries to be conducted in developed countries.*[14] This reflects the state of debate in the U.S., and the author does not think it necessarily unethical for research subjects in developed countries to be phase 1 trial subjects in their own countries for the sake of people in developing countries. The reason is that not only may one duly expect strict review of a research ethics committee and adequate procedures for obtaining the consent of

subjects in developed countries, but it ought also to be possible to provide more appropriate and advanced medical care on unforeseen developments than in developing countries. The author therefore finds it unnecessary to go so far as to change the 2004 version in this fashion.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.	**18.** Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

Commentary: Stipulating the prior assessment of risks and benefits to individuals and communities of conducting research, new paragraph 18 simplifies and reworks the substance of old paragraph 16. It is explained as recognizing the importance of communities when determining the risks and benefits of research and also including communities as well as individuals among those concerned. The second sentence of the old paragraph 16 was deemed inappropriate here and so deleted, and the third sentence moved to the following new paragraph 19, its substance broadly expanded.

	19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

Commentary: Stipulating the registration of clinical trials to make them publicly available, the new paragraph 19 is an expansion and relocation of the third sentence of the old paragraph 16. It was a noteworthy advance for the DoH to mandate the registration of all clinical studies in a database accessible by entire national populations. Rather than a mere relocation of the previous provision, this may be seen as the institution of a new one. Taking into account that some countries may not have a registration system in place or are as yet developing one, the workgroup avoided specifying the obligation in greater detail in 2008 revisions. Views may differ among countries and regions as to what research should be registered in databases and for what purpose. One of the most important reasons for instituting a database scheme is to avoid the duplication of identical research conducted on human beings by second and even third programs. Not only does medical research on human beings entail dangers and directly involve their life and physical safety, it is further an ethical requirement for research to be performed on the minimum number required.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.	**20.** Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

Commentary: A new paragraph 20 relocates more or less intact old paragraph 17 prohibiting research in which risks outweigh benefits and can not be managed. It is significant that this paragraph stipulates that research be halted where risks outweigh benefits or where conclusive proof of effectiveness and benefits has been obtained. As stated above as grounds for the registration system of the new paragraph 19, this is because of the strong trend deeming the continuation of unnecessary research to be unethical.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.	**21.** Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

Commentary: The second sentence of old paragraph 18 has been deleted in new paragraph 21, but it is essentially identical.

20. The subjects must be volunteers and informed participants in the research project.	**22.** Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

Commentary: Stipulating the terms of participation in medical research and studies by individuals capable of judgment, new paragraph 22 includes a new second sentence taking into account the special circumstances of developing countries. That the principle of the consent of the individual is not ceded so long as research subjects are capable of judgment, as a reading of the text makes clear, requires our attention. As noted in the first part of this section, the essence of this paragraph is its first sentence. This is a reaffirmation of the first proposition of the Nuremberg Code that "The voluntary consent of the human subject is absolutely essential." At the Nuremberg Doctors Trial it was questioned whether to compel non-prisoners capable of judgment held in concentration camps to participate as subjects of human experiments was a war crime or a crime against humanity.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.	**23.** Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

Commentary: With slight modification of the wording and relocated here, new paragraph 23 is essentially identical to the second sentence of old paragraph 21, which establishes the protection of the privacy, confidentiality, and physical and mental integrity of research subjects.*[15] The substance of the deleted first sentence of the old paragraph 21 is understood to be implied in the new paragraph 11. The content of this paragraph overlaps with that of the old paragraph 10 and the new paragraph 11 that elaborates on it.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.	**24.** In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

Commentary: Stipulating the information that must be provided to obtain the consent of potential subjects capable of judgment (that information necessary to obtain informed consent), new paragraph 24 is almost identical to old paragraph 22. In each case the information listed consists entirely of significant information that must be provided, and to omit to provide this information is in principle inadmissible.*[16]

	25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Commentary: A new paragraph 25 requires that the consent of the individual be obtained when collecting, using, or reusing for medical research personal data or human material that may identify an individual. This revision introduces a second sentence taking into consideration that in more than a few instances it is in reality impossible or impractical to obtain such consent and opening the way to initiate research in such cases conditional on the consideration and approval of a research ethics committee. This is an entirely new provision inserted in the 2008 revisions that was not present in previous versions of the declaration. As more than a little such research is already conducted in many developed countries, including Japan, this may be considered a provision that ratifies our reality.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.	**26.** When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

Commentary: Stipulating the consent of potential subjects in a dependent relationship with a researcher, new paragraph 26 does no more than modify slightly old paragraph 23 and is substantively much the same.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.	**27.** For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

Commentary: A new paragraph 27 has been relocated from old paragraph 24 and is restricted to subjects "of limited capacity,"*[17] while cases where a subject is competent but unable to express consent due, for example, to physical incapacitation, are relocated to new paragraph 29. New wording is inserted requiring for a subject of limited capacity the informed consent of a statutory agent or other legally authorized representative and further reinforcing the protection of subjects in the research itself.

25. When a subject deemed legally incompetent, such as	**28.** When a potential research subject who is deemed

a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.	incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

Commentary: Relocated from old paragraph 25, new paragraph 28 concerns persons deemed "incompetent" but who, even if unable to give definitive consent or non-consent, are able to express an opinion as to the pros and cons. The typical example is a legal minor of relatively advanced age. The provision requires both seeking the informed consent of a legal representative and seeking the "assent" or "dissent," i.e. an expression of disagreement, of the individual. Whereas previous versions mentioned only "assent," ought the introduction of the term "dissent" ultimately to prioritize the judgment of the legal representative, although the wishes of the individual should be respected to the extent possible, when this novel legal representative gives consent (or non-consent) and the individual expresses dissent (or assent)?

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.	**29.** Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

Commentary: A new paragraph 29 is relocated from old paragraph 26. It re-specifies, with respect to research conducted on subjects in special circumstances, such as research on unconscious patients, such matters as methods for obtaining informed consent, procedures for obtaining the consent of the individual or other person after research has commenced, content of the research protocol, and procedures for approval by a research ethics committee.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.	**30.** Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Commentary: A new paragraph 30 is an extension of old paragraph 27 specifying in greater detail than previously what content should be published and also placing stricter obligations on authors (researchers). That is, it expands the scope of reporting on research results simply by stating, in the second sentence, "Authors (researchers) have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports."

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE	C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

Commentary: Like the 2004 chapter C, the 2008 chapter C consists of five paragraphs. Aside from the incorporation of the note of clarification to paragraph 29 into new paragraph 32, the broad substantive expansion of old paragraph 30, and its changed form in new paragraph 33, old paragraph 28 is relocated to new paragraph 31, old paragraph 31 to new paragraph 34, and old paragraph 32 to new paragraph 35, all more or less intact. The text appended to the old paragraph 30 as note has been incorporated at the end of paragraph 14 stipulating the content of research protocols.

The question is whether the content of the new paragraph 32 would be more appropriately placed in chapter B or whether chapter C had to be retained as an independent chapter due to the substantive changes to the content of the old paragraph 30. This was similarly a point of discussion during the deliberations of the workgroup, and the question was left for the next round of revision so that the work of this round would proceed smoothly.

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.	**31.** The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

Commentary: To the first sentence of the old paragraph 28 specifying under what conditions it is permitted to combine medical care and medical research, the new paragraph 31 strengthens the protection of subjects by appending, "and if the physician has good reason . . . as research subjects," while also deleting the second sentence. The insertion of this new wording imposes greater rigor than did the 2000 version on the scope of such research that is permissible.

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. **Note of clarification** The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances: - Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or	**32.** The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances: • The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or*[18] • Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

Commentary: The new paragraph 32 (stipulating the utilization of placebo) is a revised text containing the substance of the note of clarification to paragraph 29.

One of the points of departure for 2008 revisions, the text is carefully crafted so as not to depart from the provisions of the noted old paragraph 29.

What met with opposition even so was the second clause of the proviso "where for compelling and scientifically . . . serious or irreversible harm."

To state it so there is no misunderstanding of 2008 revisions, unanimous approval was initially formed for the first clause.

However, approval of the second clause took its course to three-quarters of those present in the General Assembly voting yes without gaining the approval of those opposed, despite appending to it the admonition that "extreme care must be taken to avoid abuse of this option."

However, it remains a hard fact that the developing countries that are the proving grounds in clinical trials regard with striking distrust the research in developing countries led by developed countries symbolized by placebo-control studies. Dissolving the deep-seated mistrust that has arisen between developed and developing countries over provisions concerning placebo will require the developed countries to treat the people of developing countries with unfailing good faith going forward. It has become increasingly common for clinical trials in the development of new drugs to be conducted simultaneously and in parallel across national borders, including both developed and developing countries.*[19] We must heed in such cases the fact that standards of healthcare differs and ethical criteria are not necessarily uniform, as symbolized by the controversy over placebo use in short-course AZT trials. Surely Japanese researchers should learn with humility from the experience of American researchers encountering repeated controversy over various studies conducted in developing countries, not only in the host countries but also at home in the U.S.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

Note of clarification

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

Commentary: The note of clarification to paragraph 30 resulted in its substantive alteration, and as the latter half of that note was in the 2008 revisions appended to paragraph 14, the original provision is no longer needed. In view of past developments, however, the paragraph was retained in this form, recognizing, for example, the right of research subjects to learn about the outcome of a study after its conclusion. What may in fact prove to be a problem is the placement here of the phrase "entitled . . . to share any benefits that result from it."

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.	**34.** The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

Commentary: The new paragraph 34 slightly modifies the old paragraph 31 stipulating the obligation to inform patients of research conducted in the course of their treatment, but is essentially identical.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.	**35.** In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

Commentary: Aside from the deletion of the fourth sentence at the end, the new paragraph 35 is a relocation of the first through third sentences, more or less intact, of the old paragraph 32 stipulating the use of new treatments when no proven treatment is available. However, the insertion of the condition "after seeking expert advice" does make the provision more robust. The deletion of the fourth sentence is due to the provision of interpretation of the declaration in the second sentence of the new paragraph 1 that clarified its relationship with the whole.

In Conclusion

Reviewing the developments that began with the AMA draft in May 1997, led to the 2000 DoH amendments and culminated in the 2008 DoH revisions, the impression does impinge that the WMA and DoH were, against the intentions of those involved with WMA, embroiled in a domestic American controversy. On further reflection, however, what such treatment means is that the DoH enjoys the recognition of international society and is held to a high standard. The question is what expectations are held of it? At the time the DoH was instituted, all WMA member medical associations were from the developed world, and the people involved clearly generated the Declaration with the medical circumstances of developed countries in mind and as a standard for their own world. However, as things developed thereafter, particularly from the 1980s forward, numerous medical associations from middle-income countries and developing countries joined the WMA, and participants were now from strikingly different social, cultural, and economic backgrounds. The result was that it has been extremely difficult, and sometimes impossible, for these global representatives to impose a uniform controlling standard. Even so, it is necessary, in so far as that context permits, to formulate a single common standard to safeguard the health and the best interests of patients and research subjects.

The incidence of randomized placebo (no-treatment) controlled research (studies) spanning multiple, numerous countries has increased rapidly in recent years. Whether one takes the position that all such research is unethical or not necessarily so, I believe that it is incumbent on us to maintain an ongoing discussion within the WMA as to what should be deemed unethical,

and in what cases, in research conducted domestically and internationally, and especially that conducted in both developed and developing countries.

Immediately following the Seoul General Assembly, the WMA Council formed a new work group within the MEC to engage in earnest with the issue of placebo-controled trials raised by developing countries. The workgroup's proposal to the Council Session in Tel Aviv in 2009 was approved for holding a symposium with a medical ethics perspective in Brazil in February 2010 with the aim of unifying the standards of CIOMS, UNAIDS, the ICH-GCP, the Nuffield group, and others.

Acknowledgements

I would like to thank officers of JMA, Dr. Y Karasawa, President, Dr. K Iwasa, Vice-President, Dr. M Ishii, Executive Board Member and Editor-in-Chief of JMAJ, and its staff, Mr. H Tsuruoka, Ms. S Koyanagi, Ms. M Hamamoto, Ms. M Imamura, and Mr. S Uchiyama for their assistance in developing this report.

Endnotes

*2 An eminent professor of internal medicine and pharmacology at Yale University, Levine is also a scholar of medical ethics. While serving successively on various US governmental and UN commissions, in 1989 he was also installed as president of the American Society of Law & Medicine (now the American Society of Law, Medicine & Ethics) and has long served as chief editor of the society's journal. His involvement with the DoH came about through his role, in collaboration with the UNESCO-affiliated CIOMS and WHO, as a leading author in drafting and compiling the 1993 and 2002 editions of the International Ethical Guidelines for Biomedical Research Involving Human Subjects addressing concerns in the developing world. In an address titled "Multinational Clinical Trials of New Drugs and Vaccines: Ethical Challenges" delivered as an invited speaker at the 20th meeting of the Liaison Society of Ethics Committees in Medical School in Japan held in Kyoto in September 1998, Levine raised problems with the DoH and stated the need for its broad revision. He also published in the *NEJM* an article titled "The Need to Revise the Declaration of Helsinki."[5]

In response to the AIDS epidemic then rampant in sub-Saharan Africa, the Caribbean, and South Asia, in June 1994 the WHO led the planning, with backing from UNAIDS, the American and French governments, and others, of clinical trials to ascertain the effectiveness of treatments employing the anti-HIV drug zidovudine (AZT) in one-tenth doses and over greatly reduced periods of time (short-course, reduced-dose AZT regimens) in order to prevent mother to infant HIV transmission and develop less expensive prophylactic methods. A panel of experts organized by the WHO and including Levine concluded that randomized placebo (no-treatment) controlled studies would be needed to reach valid scientific conclusions within a short period of time. Clinical trials were conducted in various locales, concluding when a Thai study conducted in January 1998 confirmed infant HIV infections among the one-tenth dosage group were only one-half those among the placebo control group.

It was in reaction to this research that Angell, Lurie, and Wolfe published articles in the *NEJM*, attacking the clinical studies conducted with the backing of the WHO, US government, and others as unethical because newborns assigned to placebo groups were put at an unnecessary disadvantage.[2,6] James V. Laveery, et al., describe the critics and the thrust of their argument thus:

> Finally, these critics argued that the placebo-controlled trials of short-course AZT violated the Declaration of Helsinki, a major source of ethical guidance on research ethics around the world. In 1997, the Declaration of Helsinki stated that
>
> > [i]n any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic methods.
>
> Lurie, Wolfe, and Angell argued that this provision required researchers to provide the control long-course AZT as the 'best proven' therapeutic treatment.[7]

Supporters of the research replied that the short-course AZT trials were planned with the objectives of investigating whether a short course of AZT in reduced doses would be effective and, if successful, of utilizing the treatment in developing countries lacking the financial resources to purchase the extremely expensive AZT in the volume conventionally required, and that conducting the research in the context of such scarcity meant that it was mistaken to see things in terms of the wealthy U.S. In that the criticism of design of experiment by the

Lurie-Wolfe paper was accompanied by an assertion of the means of ascertaining the utility of short-course AZT regimen with reduced doses without opting for placebo (no-treatment) groups,[2] the summary above of Laveery et al. is not above reproach.

However the case may be, it would be altogether too simplistic and rash to use ritual quotations of DoH provisions to attack a research program devised—unlike those conducted by private firms for purposes of enrichment—by the WHO, the U.S. government, and others to help the people of developing and impoverished countries with meager aid monies while ignoring the conditions (the economic ones, in particular) imposed on its designers. There is no denying that where research involves both developed and developing countries, some schemers may find a way to abuse DoH standards. All the same, those wont to abuse them will find a way to do so, however commendable the rules one might draw up. Our task, therefore, ought rather to be finding ways to avert their abuse.

Levine's 1999 paper was both a reply to the criticisms of Angell et al. of 1997 and a strong assertion of the need to revise the DoH. Given this background, the U.S. controversy over short-course AZT and placebo controls may be seen as what triggered the 2000 DoH revisions.

*3 Dr. Sakanoue, a member of the workgroup in 1998, asked NMAs at that time how they understood clinical and non-clinical research. He received the following reply from Prof. J.R. Williams, who was then the Canadian Medical Association ethics officer:

> As I suspect is the case in most other countries, in Canada the term "clinical research" does not have one precise definition. There is a range or spectrum of medical research activities with those that are clearly non-clinical at one end (for example, in-vitro pharmacological or large-scale epidemiological studies) and those that are clearly clinical (for example, clinical trials of new drugs or surgical procedures) at the other end. It is very difficult to find a dividing line between the two. Research involving human gametes, embryos and fetuses might or might not be considered clinical research depending on where the dividing line is drawn. My personal view is that if the study is primarily biochemical or epidemiological in nature, which I believe is presently the case with studies on gametes and embryos, it should be considered non-clinical research. However, if the primary aim of study is to test a treatment for an illness or disease, whether or not the research subject is affected by that illness or disease, then it should be considered clinical research. Research on fetuses would probably fall into this category.

*4 Held in April 1999 to mark the seventieth birthday of Göttingen University Prof. Deutsch and attended by scholars from throughout the world associated with him, this symposium at Göttingen University addressed the Levine draft. The symposium was led by Prof. Jochen Taupitz, director of the Institute for German, European and International Medical Law, Public Health Law and Bioethics (IMGB) at the Ruprecht-Karls-University of Heidelberg and the University of Mannheim. After hearing reports on DoH implementation in participating countries, the full attendees discussed the Levine draft clause by clause. On the final day, the issues that had emerged were compiled into a 20-point report (the Göttingen paper) that was presented to the 153rd WMA Council Session in Santiago, Chile, in April of that year. Expressing the opinion of influential medical law scholars from Europe, the U.S., and Asia, the report is considered to have had a great influence on the formation of opinion in the Council. The author participated in the symposium together with Prof. Michitaro Urakawa, who reported on the situation in Japan. (The symposium's report is included as the "Göttingen paper" at the end of Deutsch and Taupitz, "Freedom and Control of Biomedical Research."[8])

*5 The 153rd WMA Council Session of April 1999 issued the following recommendation on establishing the new workgroup.

1. That Working Group on the Revision of the DoH be thanked for drafting a proposed revision and for compelling its task.
2. That a new Working Group comprised of Dr. Nancy Dickey (USA-Chairperson), Dr. Judith Kazimirski (Canada) and Dr. Kati Myllimäki (Finland) be established to analyze the existing information on the DoH and to coordinate further action, under the supervision of the Medical Ethics Committee.
3. That national experts and other representative groups continue to provide input, but that their opinions and suggestions be submitted directly to the NMA in their country. The views submitted to the WMA Working Group should represent the official views of the NMA.
4. That NMAs be given an additional six months to provide comments.

   The comments should:

   a) Identify specific concerns regarding terminology, concepts and structure in the original DoH and the previous Working Group's proposed Revision;
   b) Provide explicit suggestions for revision of the areas identified;
   c) Include interpretations of the following terms: Biomedical Research Involving Human Subjects;

Clinical Research; Non-Clinical Research; and Compassionate Care.

*6 As is clear from the foregoing, the 1997 AMA draft and the Levine draft to which it gave shape had their origins in criticism of the dichotomy in the DoH framework of clinical and non-clinical research. For the countries of central Europe with a tradition of Continental law, the AMA draft that would do away with the DoH framework built on the premise of a traditional distinction between fault liability and no-fault liability was, as seen in the contrary view immediately set forth by Prof. E. Deutsch, in some sense a revolutionary proposition, and it was natural for the bulk of the initial opposition to it to concentrate on that issue. As Levine says, however, whether clinical or non-clinical, research lies on a continuum, and from the perspective of protecting research subjects, it is both forthright and fair to apply a single standard to its conduct.

The impression held by the author is that it is inherently wrong to ground the jurisprudence of compensation for damages in this duality. (I rather suspect that the true motive for distinguishing clinical and non-clinical research was to leave practicing physicians broad discretion by regulating the former more lightly than the latter.) Setting that aside for the time being, the author does consider absolute liability or no-fault liability appropriate to the redress of aggrieved parties in research, whether sponsored by a pharmaceutical firm or other private enterprise or by the state, and my belief is that the direction taken by the AMA draft proposing abolition of the distinction is not a mistaken one. Therefore, I am in agreement with establishing a single fundamental standard. Considering actual cases, after all, there is a long-standing distinction between patient subjects who participate in research for care and healthy subjects who participate in research voluntarily or for compensation. That it was necessary to include in the 2000 DoH that would have abolished this dichotomy the text of "C. Additional Principles for Medical Research Combined with Medical Care" shows that in reality one is not always able to apply a single standard.

Be that as it may, during the two years and more of accrued discussion within and without the WMA, the dispute as to whether the dichotomy was right or wrong that was the major point of contention between the United States and Europe quietened, and the focus of people involved with WMA shifted entirely unexpectedly to the issue of placebos. With hindsight, the original aim of the AMA draft was to revise the placebo provisions, and the proposal to abolish the distinction between clinical and non-clinical research may have been a collateral issue. Evidence of this is that the FDA has continued to this day to use the 1989 DoH, which is grounded in the dichotomy. (See note 8.)

*7 According to the presentation to the WMA Helsinki General Assembly in September 2003 by Dr. Robert Temple, the FDA's Director for Office of Medical Policy and its Center for Drug Evaluation and Research, he considers clinical trials conducted in the U.S. in the development of new drugs to satisfy DoH ethical requirements because such clinical research is subject to making an "Investigational New Drug (IND) Application" in accordance with Part 21:50.56 of the Code of Federal Regulations (CFR), which substantially incorporates the DoH, and such requirements would be satisfied so long as clinical studies are conducted with the IND application made. He stated that acceptance of data from clinical studies conducted overseas without making an IND application as for domestic sales applications or clinical studies data is governed by the CFR 312:120 regulations, which cite the DoH and require the submission of evidence that those clinical studies were DoH-compliant; and that the DoH ultimately cited in that regulation in the 1989 version and that later versions have problems and were not in use.[9]

*8 The amendments to the DoH in Tokyo in 1975 were the first in ten years and resulted in extensive growth in both content and paragraphs. To distinguish it from the initial declaration, the 1964 declaration is sometimes called Helsinki I and the Tokyo declaration is called Helsinki II or the Tokyo DoH revisions. Helsinki II underwent partial minor revisions in 1983 in Venice, in 1989 in Kowloon, and in 1996 in Somerset West. Thus, although the 2000 revisions should be called Helsinki III in terms of substance, they are sometimes referred to as Helsinki VI in terms of sequence.

*9 The WHO recognized the DoH as a set of international guidelines at an extremely early point, recommending its adoption as ethical research guidelines in developing countries. According to the Background Note in "International Ethical Guidelines for Biomedical Research Involving Human Subjects" by the WHO-CIOMS collaboration, "The DoH promulgated by the WMA in 1964 is a basic text in the field of ethics in biomedical research and is indicative of how effectively ethical principles to guide its conduct internationally, regionally, and domestically may be applied, particularly in developing countries, provided with their socioeconomic environment, laws and regulations, and governmental and administrative arrangements."[10] The U.S. regulation mentioned in note 7 was last revised 18 June 1991. As of end-July 2008, the 1989 DoH remains in use.

Additionally, as articulated in note 10, the ICH-GCP guidelines prescribe that "clinical trials must be con-

ducted in accordance with ethical principles having their origins in the DoH." With this agreement, the governments of many developed countries came to specify DoH compliance in their domestic laws concerning drug development. (Although more than a few use the 1996 version, however, there is no consistency in the version used.) The Japanese government revised the Pharmaceutical Affairs Law in the year following the ICH-GCP agreement and stipulated a ministerial ordinance titled "Clinical Drug Trial Standards (GCP)." This ministerial ordinance renders the ICH-GCP agreement faithfully in statutory form. However, there is no mention of the DoH in the ministerial ordinance. Instead, administrative guidance titled "Application of Standards for the Implementation of Clinical Trials on Pharmaceutical Products" issued within the framework of the law that orders at its outset compliance with ethical principles based on the DoH and with the standards stipulated in the ministerial ordinance.

*10 To arrive at uniform standards and methods for examining and registering drugs, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use in May 1996, made of delegations from the EU, Japan, and U.S. governments, instituted at its Yokohama conference the ICH-GCP guidelines as a uniform international standard, and their various national governments agreed to employ these guidelines.

The Introduction of the guidelines states:

> Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects, safety and well-being of trial subjects are protected, consistent with **the principles that have their origin in the Declaration of Helsinki**, and that the clinical trial data are credible.

In section 2 "The Principles of ICH-GCP," item 2.1 specifies as follows:

> Clinical trials should be conducted in accordance with **the ethical principles that have their origin in Declaration of Helsinki**, and that are consistent with GCP and the applicable regulatory requirement(s).

The problem is that the DoH at the time of the Yokohama agreement in 1996 was the 1989 version, which contains no provisions concerning the use of placebos and no-treatment courses.

It was at the Somerset West General Assembly in October 1996 that the placebo provision below appeared, and it would not be a stretch for government officials and researchers from, e.g., the U.S. to consider this provision inserted with the purpose of markedly restricting the use of placebos. The proposal for the insertion of the placebo provision in 1996, as it happens, was WMA President Prof. Kincaid Smith (Australia), but it is not certain that she did so with the intention of restricting placebo use.

> 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.

As is seen from a comparison of the second sentence of paragraph 29 in the 2000 DoH and the second sentence of paragraph 3 in the 1996 DoH, the text is substantially the same and it must be said that the U.S. government (FDA) officials have a point in their negative reaction to the 2000 revisions.

*11 The author has for some time contended that the DoH is not a manual, nor should it be used as one. DoH compliance is incorporated into the ICH-GCP guidelines, and it is a fact that it has influenced domestic law in the countries concerned. Even granting that premise, however, the DoH is in the end a WMA declaration. To read and interpret it stringently as though it were a legal text is going too far. As well as being a declaration, it contains aspirational targets for the future; paragraph 30 may be read as such. Understood as what lawyers call provisions of a program or manifesto, it is quite usable as is.[11]

*12 In an expert opinion titled "The German Perspective" drafted for the German Medical Association when DoH revisions were submitted via the AMA draft in 1997, Prof. Deutsch emphasizes that its coverage should be limited to physicians: "VIII. Physicians and Other Research Investigators: While the current Declaration of Helsinki addresses itself to physicians only, the proposed new version is going to include other research investigators as well . . . . The declarations of the World Medical Association are supposed to become the ethical standards of persons who have founded the World Medical Association and are subject to its declarations. These are just physicians. To enlarge the Declaration of Helsinki on non-medical investigators is simply ultra vires."[1] While recognizing the viewpoint, the author considers it altogether too legalistic an argument.

*13 In Japan, where employ a system of lex scripta, the study of law begins with instruction in the methods with which to interpret legislative language and other such texts. Wagatsuma teaches, for example, that there are various kinds and methods of interpretation:

> Various techniques exist for the interpretation of the Civil Code. *Grammatical interpretation* follows the normal meaning of the letter of the text, while *logical*

interpretation construes the Civil Code as constituting a single logical system and seeks to assign each of its provisions their due status and furnish them congruence. Given two similar instances A and B where provision is made for A only, *argumentum e contrario* admits of outcomes for B contrary to that for A, whereas *analogy* admits of outcomes for B similar to that for A. However, such a catalog of the techniques of interpretation does not in fact assist interpretation. The logical system on which logical interpretation is premised may be constructed according to formal logic, or it may be constructed according to purposive logic . . . . The one thing to remember is that the interpretation of the Civil Code has two missions. The first is to furnish to the laws of the Civil Code substance of a general certainty such that outcomes do not vary with the personalities or the case in question, and the second is to furnish to the laws of the Civil Code an objective validity such that they provide valid outcomes in their several applications. General certainty and objective validity are the two missions of the legal code, but they are of especial significance with respect to law that orders civil life, such as the Civil Code.[12]

The points Wagatsuma makes here are likewise pertinent to the interpretation of the provisions of an ethical declaration such as the DoH. In interpreting the provisions of the DoH, by the way, more than a few persons engaged in the discussion in the United States, in particular, are engaged in extreme grammatical interpretation of lone individual provisions in isolation. The purpose of the insertion of the second sentence in the revised 2008 paragraph 1 was to rebuke the extreme grammatical interpretation that was argument for the sake of argument.

*14 When asked about the meaning of the limitation, the drafter's response was to refer to the series of papers found under "Testing a Phase 1 Malaria Vaccine" of James V. Laveery et al., Ethical Issues in International Biomedical Research. According to these papers, when a phase 1 trial of a vaccine developed in the U.S. was conducted on people in the U.S. with FDA grants in order to assist the people of the Republic of Mali, which had suffered the deaths of numerous adults and children from malaria, paragraph 19 of the 2000 DoH was cited to describe the research (the Baltimore Malaria Vaccine Study) as unethical due to the conduct of the phase 1 trial in the U.S. where no one could expect to benefit from it.[7]

A topic raised in these papers is "the exploitation of rich Americans by impoverished Malians." A section by Bernard Dickens introduces the view that, for reason of the one sentence in the old paragraph 19 of the DoH, "Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research," a phase 1 trial conducted in the U.S. where an affected population was not present could not be justified and would be judged unethical, but the author is unable to see how the text of that paragraph 19 could lead to such a conclusion. The argument that a phase 1 trial conducted in a developed country for the sake of a developing country would violate that paragraph 19 can only be reckoned argument for the sake of argument, an interpretation attending only to the superficial text of that paragraph 19 without considering the import and background that gave rise to the DoH or the CIOMS guidelines.

*15 I think that Japanese can easily appreciate that physicians have a duty to protect the privacy and confidentiality of research subjects and patients, but the term of protection of the "integrity" of subjects and patients is a concept unfamiliar to us. I understand that this shares common ground with the idea of the inviolability of the individual (will and dignity) declared in terms of "The voluntary consent of the human subject is absolutely essential" at the outset of the Nuremberg Code.

*16 The information listed in the new paragraph 24 as required when obtaining informed consent is incorporated into the ICH-GCP and is also employed in the ministerial ordinance GCP based on the Japanese Pharmaceutical Affairs Law. Furthermore, the content of paragraph is also incorporated into clinical research and other guidelines prepared as administrative guidance in Japan that also express adherence to the DoH.

*17 Article 20 of the Japanese Civil Code stipulates thus: "persons of limited capacity (minors, adult wards, persons under curatorship, and persons under guardianship by the court finding of Article 17, paragraph 1)." The term "minors" in parentheses is defined as persons under 20 years of age (cf. Civil Code, Art. 4); the term "adult wards" as "'persons of normal condition lacking the capacity to discern right and wrong due to mental disability' deemed adult wards by judgment of family court"; the term "persons under curatorship" as "'persons of extremely insufficient capacity to discern right and wrong due to mental disability' and deemed subject to curatorship by judgment of family court"; and "persons under guardianship by the court finding of Article 17, paragraph 1" as "'persons of insufficient capacity to discern right and wrong due to mental disability' and deemed subject to guardianship by judgment of family court." As this makes clear, in a strict sense "persons of limited capacity" according to the Civil Code refers,

excepting legal minors, to persons found by judgment of family court to be "adult wards," "persons under curatorship," or "persons under guardianship." When we translated the 2008 DoH into Japanese, we have borrowed the legal term "persons of limited capacity" because no other appropriate term is available in Japanese, but we should think of this as protecting all "'legal minors,' 'persons of normal condition lacking the capacity to discern right and wrong due to mental disability,' 'person of extremely insufficient capacity to discern right and wrong due to mental disability,' and 'persons of insufficient capacity to discern right and wrong due to mental disability.'"

*18 The expression "where no current proven intervention exists" is certainly a subtle one. As argued with respect to short-course AZT regimens, the application of developed-country standards and developing-country standards yields different answers. That aside, the questions remain as to who certifies, for a given state of illness, whether "no current proven intervention exists" and, if it were possible to certify such, whether a protocol administering an investigational new drug to one group and assigning another to a no-treatment course would be an ethical one. For example, when conducting research on a second-line combined therapy involving a new anti-cancer drug because the first-line chemotherapy proved ineffective against an advanced and recurrent cancer that is incurable and unresectable, might it somehow be termed ethical under the terms of this paragraph to conduct research with some subjects assigned to a randomized no-treatment course?

*19 Although attention has focused entirely on the relationship between developed and developing countries in the discussion to this point, the point has been made that the greater issue may lie between high-income and middle-income countries. It is a fact that in both high-income and middle-income countries, although a well-off country may have accomplished welfare policies and ready access to healthcare for its entire population, some of them contain large numbers who experience difficulty gaining access to healthcare. It is a problem in these countries that people considered as healthcare refugees enroll in clinical trials seeking to enjoy the blessings of advanced medicine. I believe that we need to continue to discuss this issue in the future.

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