

Declaration of Helsinki Expert Conference on the Ethics of Placebo Control in Clinical Trials—Comments on the “reasonable availability” approach*¹

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Introduction

Revisions to Declaration of Helsinki (DoH) 2004*⁴ were adopted at World Medical Association (WMA) General Assembly held in Seoul, South Korea in October 2008. As strong opposition was expressed by Brazilian Medical Association on behalf of developing countries to the new second conditional clause of Paragraph 32, which concerns placebo-control trials, this paragraph was approved with a majority of more than three-quarters.¹ The other paragraphs were approved unanimously including Brazilian Medical Association.

Paragraph 29 [DoH 2004]

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*
- *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.*

Paragraph 32 [DoH 2008]

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*
- *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.*

*¹ This article was based on the presentation made at Expert Conference on Ethics of Placebo Control in Clinical Trials hosted by World Medical Association in São Paulo, Brazil in July 13–15, 2011.

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*⁴ WMA General Assembly added Note of Clarification on Paragraph 29 in 2002 and on Paragraph 30 in 2004, respectively. The other paragraphs of DoH 2000 were not revised until 2008.

In light of these events, at the council meeting held immediately after Seoul General Assembly, a working group was established within WMA Medical Ethics Committee and was entrusted to seriously examine this issue to enable the formation of a sincere response to the opposition of Brazil and other member countries. This new working group comprised the same members as the working group that had formulated the 2008 revision proposal, with Japan Medical Association (JMA) continuing to participate as a representative of Asia. German Medical Association undertook the preparatory summary work for the new working group.

At WMA Council Meeting held in Tel Aviv in May 2009, approval was given to invite specialists from World Health Organization (WHO), Council for International Organizations of Medical Sciences (CIOMS), National Institute of Health (NIH), and other health organizations to participate in an expert conference aimed at achieving uniform standards for placebo-control trials. The first expert conference was held for three days from February 1, 2010 in São Paulo, Brazil. At WMA Council Meeting held in conjunction with WMA Vancouver General Assembly (Canada; October 2011), it was decided to hold the second expert conference for three days from July 10, 2011 in Tokyo, Japan. Here the working group was to formulate its final revision to the proposal to be presented to WMA General Assembly in Montevideo, Uruguay, in October of the same year. With this, the task of the working group was to have been completed. However, the occurrence of Great Eastern Japan Earthquake on March 11, 2011 made it difficult for JMA to host this meeting, and through the kindness and generosity of the Brazilian Medical Association, the second expert conference was held in July, 2011, at the University of São Paulo Faculty of Medicine (San Paulo, Brazil).

The theme prepared by German Medical Association for this meeting was divided into two parts. The Part I discussed the main issue, the “General wording of Paragraph 32 of the Declaration of Helsinki.” However, no consensus could be reached with regard to the necessity of revising Paragraph 32 or the direction of such revision. Therefore, this issue is left for further consideration in the future.

Part II examined “International clinical research and the use of placebos in resource poor

settings,” focusing on the issue of serious conflicts of interest between developed and developing countries in clinical research on an international scale. The discussion directly faced the fact that, when a developed country with money sponsors a clinical research which experimental trials are carried out in a developing country, the research results are often used solely for the benefit of the developed country and are not shared with the developing country. Such cases have occurred in placebo-controlled studies as well, and the conference participants sought solutions to this problem.

As commentators for Session 4, the authors made a presentation concerning the “reasonable availability” approach, as summarized below.

Status of Implementation of DoH in Japan

Currently in Japan there are two kinds of standards pertaining to “clinical research involving human subjects.” The first of these comprises provisions based on Pharmaceutical Affairs Act. With the establishment in May 1996 of International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice (ICH-GCP) standards among Europe, the United States, and Japan, the Japanese government (namely, the then Ministry of Health and Welfare) revised the 1996 Pharmaceutical Affairs Act, prescribing the ministerial ordinance on Good Clinical Practice (GCP) for Drugs (“the GCP Ordinance”) that took effect as of March 1997. Those seeking approval for the manufacture or sale of pharmaceuticals are required to perform clinical trials in accordance with these standards. These are the current standards and are based on the law.

Other standards pertaining to “clinical research involving human subjects” are based on administrative guidance from the Japanese Government. That is to say, there are no legally prescribed regulations in Japan pertaining to any clinical research on humans apart from those conducted in accordance with Pharmaceutical Affairs Act. However, the Japanese government has formulated five ethical guidelines: “Ethical Guidelines for Human Genome and Genetic Sequencing Research” (March 2001), “Guidelines for Clinical Research on Genes” (March 2002), “Ethical Guidelines for Epidemiology Research” (June 2002), “Ethical Guidelines for Clinical Research”

(July 2003), and “Guidelines for Clinical Research Using Human Stem Cells” (March 2006). Medical and pharmaceutical researchers must comply with these guidelines through a range of administrative guidance.

Of these guidelines, in their preambles “Ethical Guidelines for Epidemiology Research” and “Ethical Guidelines for Clinical Research” require that all researchers conduct research in accordance with WMA Declaration of Helsinki, etc. Moreover, these guidelines have undergone repeated revisions to adapt their content to current circumstances of the time. For example, in July 2008 “Ethical Guidelines for Clinical Research” underwent major revisions which went into effect in April 2009. Newly prescribed directives included researchers taking measures to provide compensations for any health damage incurred by trial subjects in accordance with researcher responsibility. In the case that the research involves invasive procedures, the research leader of a clinical trial must record the research plan (protocol) in a database as prescribed by the national government (The access to the database is limited to those established by National University Hospital Council of Japan, Japan Pharmaceutical Information Center, and Japan Medical Association). It should be noted that the content of these guidelines is being modified according to the movements of DoH 2008 adopted in Seoul.

The Reasonable Availability Approach

The task that we were set in the WMA expert conference was to comment on the appropriateness of the “reasonable availability” approach, which derives from the phrase “... any intervention or product developed, or knowledge generated, will be made reasonably available for the benefits of that population or community” used in “International Ethical Guidelines for Biomedical Research Involving Human subjects,” published by CIOMS in 2002,² in relation to the debate and criticism of “ethical export” and “research on the poor to benefit the rich.”

Reports on this issue have been published, including “Moral Standards for Research in Developing Countries: From ‘reasonable availability’ to ‘fair benefits,’” which was published in the Hasting Center Report 17.³ As its subtitle indicates, this report rejects the “reasonable availability” approach, asserting that it is the “fair

benefits” approach that is correct. The beginning of this report states:

There seems to be general agreement that “reasonable availability” is necessary in order to ensure that the subject population is not exploited.

This consensus is mistaken, however. A “fair benefits” framework offers a more reliable and justifiable way to avoid exploitation.

The report then goes on to state that:

The fundamental problem with the reasonable availability standard is that it guarantees a benefit—the proven intervention—but not a fair level of benefits, and therefore it does not necessarily prevent exploitation. Reasonable availability focuses on what—the products of research—but exploitation requires addressing how much—the level of benefit. For some research in which either the subjects would be exposed to great risks or the sponsor stand to gain enormously, reasonable availability might be inadequate and unfair. Conversely, for very low- or no-risk research in which the population would obtain other benefits, or in which the benefits to the sponsor are minimal, requiring the sponsor to make a product reasonably available could be excessive and unfair.

The report further details six other points as the problems with “reasonable availability standard.” The second point states that CIOMS only considers successful Phase 3 clinical trials and ignores Phase 1 and Phase 2 trials. The report points out that CIOMS’s main concern is successful Phase 3 clinical trials, and that is certainly a major problem. As is well-known, numerous clinical trials are being held all over the world, but in an extremely high number of cases Phase 1 and 2 clinical trials are discontinued. Moreover, the fact remains that even if clinical trials finally reach Phase 3, not all of them will produce successful results.

We do not regard “reasonable availability standard” as being totally erroneous. However, we submit that the “fair benefits” approach is superior to the “reasonable availability” approach, for it thoroughly weighs the pros and cons of “benefits and non-benefits” of all parties involved in the research in question and requires an appropriate conclusion.

Paragraphs 33 and 17 of DoH 2008

Paragraph 17 of DoH 2008 was a modification of Paragraph 19 in DoH 2004.

Paragraph 19 [DoH 2004]

Medical research is only justified if there is a reasonable likelihood that populations in which the research is carried out stand to benefits from the result of the research.

Paragraph 17 [DoH 2008]

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 benefits from the result of the research.

At the time of the 2000 Edinburgh revision, when the former Paragraph 19 was established, Dr. Jochen Taupitz of University of Mannheim pointed out that this paragraph was established in order to prevent the “exploitation” of the people of developed countries by developing countries that may use the disparities in ethical and medical standards to their advantage when conducting multinational research that involve both developed and developing countries.⁴ His comment on Paragraph 19 is as follows.

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 “population” 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.

As this comment clearly indicates, regardless of whether or not this was a complete solution to the problem, DoH tackled the problem of ethical export face to face, achieving resolution to some extent in this form. Except for some additions, the text of Paragraph 17 of the DoH 2008 in practical terms has the same meaning as that of the 2000 version, which resolved the issue of exploitation.

However in DoH 2008, Paragraph 33 was added after Paragraph 32 to further strengthen

the position of trial subjects.

Paragraph 33 [DoH 2008]

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.

Considering the circumstances described above, the problems of ethical export and exploitation can be regarded as having basically been resolved with regard to DoH 2008. Accordingly, we believe that there is no need to discuss any further revision of DoH at this moment, except Paragraph 32. As previously stated, the working group, which was entrusted to examine the issue of placebo-control trials, could not reach consensus at the second expert conference in São Paulo. Thus, the issue of revising Paragraph 32 still require further debate.

Implications

In its preamble, DoH reaffirms the content of WMA Declaration of Geneva and International Code of Ethics, calling again for the protection of clinical trial subjects and consideration of disadvantaged or vulnerable people. Thus under DoH the exploitation of clinical trial subjects in clinical research is regarded as something that should not occur, and this stance is only natural.

The main discussion considered in this conference was the prevention of exploitation of developing countries by developed countries. However, exploitation also occurs between and within developed countries. When speaking of a “disadvantaged or vulnerable population or community,” our eyes tend to turn to the people that comprise local communities and those in developing countries. However, we must not forget that regardless of whether a country is developed or developing, there exists within its population people who are sick or injured—especially those with severe conditions who are in financial difficulty—and, those people are “disadvantaged or vulnerable” people as well. Unlike relationships between developed and developing countries, seriously ill patients cannot even act as a—and in that sense, we can even call them the “weakest of the weak.”

In any case, in clinical research involving human subjects, no one should be unilaterally disadvantaged, and conversely, no one should

gain enormous individual benefits through the sacrifice of others.

Postscript (as of November 8, 2011)

1. The report above summarizes the statements made by the authors as commentators during “Session 4: The ‘reasonable availability’ approach” in “Part II: International clinical research and the use of placebo in resource poor settings” of International Expert Conference on Ethics of Placebo Control in Clinical Trials, which was held for three days from July 13th, 2011 at University of São Paulo, Brazil.
 - (1) At this meeting, German Medical Association, which was in charge of the working group, submitted a proposal for revision to Paragraph 32 of DoH, and specialists who had been invited as advisors also had an opportunity to voice their opinions. The proposed revision added the phrase “any intervention less effective than the best proven one, placebo (or no treatment)” and other words to two parts in the second conditional clause, and also added the sentence “The use of any intervention less effective than the best proven one, placebo, or no treatment, is acceptable in studies where both conditions above apply and research is necessary to develop a treatment option adapted to local health care resources and health priorities” at the end of the second clause. (Alternative wordings were also suggested.)
 - (2) It is widely known that Dr. Robert Temple of U.S. Food and Drug Administration (FDA) expressed strong objections when the Edinburgh revision was made, a revision which guaranteed that patients who participate in a study to which Paragraph 29 on placebos and Paragraph 30 on research results apply receive the treatment shown to be best by the said study. Brazilian Medical Association also opposed the second conditional clause of the new Paragraph 32, which corresponds to Paragraph 29 of the Seoul revision, and insisted upon deleting the said part. As a result, the sentence “Extreme care must be taken to avoid abuse of this option” was inserted at the end of the second conditional clause, based on the suggestion made by Dr. Hill, the chairman of the council.
 - (3) At the previous International Expert Conference on Placebo Control in Clinical Trials hosted by Brazilian Medical Association that was held in São Paulo for three days from February 1, 2010, Dr. Temple shared his observation that, unlike the old Paragraph 29 of the Edinburgh revision, Paragraph 32 of the Seoul revision was no different from the ICH-GCP10. Dr. Hill, the chairman of the council, recapitulated that the new Paragraph 32 should not be modified. Dr. Temple also participated in 2011 Expert Conference and expressed various opinions. The section that Dr. Temple questioned was, as expected, Paragraph 33 (, which corresponds to Paragraph 30 of the Edinburgh version) and its associated clauses.
2. The working group reported the results of the expert conferences to WMA Medical Ethics Committee when it met in Montevideo, Uruguay, on October 12, 2011. Partial revision of Paragraph 32 was discussed at this meeting. This concluded the task of the working group, which had spent two years on discussion of the placebo issue.
 - (1) WMA General Secretariat announced that, because the year 2014 marks the 50th anniversary of DoH, it will ask for approval at the council meeting in 2012 to establish a new working group under Medical Ethics Committee to comprehensively review DoH. The announced plan is to update the content of DoH and make revisions as a 50th anniversary project.
 - (2) The updating of DoH to meet the demands of the times is expected to begin, and the task of preparing for the update is to start at the working group level next year. However, it is advisable to reaffirm the nature of DoH in that it is meant to express fundamental principles.

References

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