

EDITORIAL

The Declaration of Helsinki: another revision

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Only eight years after a major revision of the Declaration of Helsinki (DoH), this highly regarded document providing ethical guidance for research involving human beings (1,2) has now undergone another revision (3). This prompts the question why the World Medical Association (WMA), which issues the Declaration, decided to make changes again so soon. One can only speculate whether powerful forces exerted pressure on the WMA to change some key provisions that were viewed as unfriendly to industry and other major sponsors of multinational research. The 2008 revision strengthens the previous version in some respects and weakens it in others. The most salutary improvement is in the paragraph that stipulates when it is ethically acceptable to use placebos in a control arm of a randomised, controlled clinical trial.

A first, somewhat skeletal version of the Declaration was issued in 1964, followed by expansion and a series of amendments beginning in 1975. The amendments from 1975 through 1996 were relatively minor. A notable change occurred in 1996, when a paragraph that was to become highly controversial was amended from the previous 1989 version. The latter version contained the following clause relating to the design of a research proposal: "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." In an amendment to the Declaration in 1996, the following statement was added to that paragraph: "This does not exclude the use of placebo, or no treatment, in studies where no proven...method exists." At the time, this paragraph did not attract attention nor did it give rise to any debates. It was only after controversy erupted in 1997 over placebo-controlled, mother-to-child HIV transmission trials carried out in developing countries that world-wide attention focused on the Declaration of Helsinki's prohibition on the use of placebos when a proven method exists somewhere in the world. When the HIV trials were publicly criticised (4), but also strongly defended (5), calls emerged seeking a revision of the Declaration of Helsinki (6). In a process that took place over several years involving some inner turmoil, yet at the same time a degree of transparency, the WMA issued a significantly revised version of the Declaration in 2000.

Along with other paragraphs that gave rise to some controversy, the one that attracted most attention was the new Paragraph 29, which basically reiterated the statement in the 1996 version: "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." A major opponent was the US Food and Drug Administration (FDA), the regulatory agency that strongly favours the use of placebo controls in studies submitted to the agency for drug approvals. Most recently (2008) the FDA issued new regulations that abandoned its previous rule that foreign studies must comply with the provisions of the Declaration of Helsinki (2). The FDA's new regulation replaced the DoH with the International Conference on Harmonization (ICH) Good Clinical Practice Guidance (GCP) (7), which has a much weaker provision regarding the use of placebo controls in clinical studies. In November 2001 the World Medical Association published what it called a "clarification."

Note of clarification on Paragraph 29 of The WMA Declaration Of Helsinki

The WMA is concerned that paragraph 29 of the revised Declaration of Helsinki (October 2000) has led to diverse interpretations and possible confusion. It 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.

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

Not only did this addition fail to “clarify” the paragraph: the first of the two conditions simply reopened the door to the very controversy that led to the revision of the Declaration in the first place. The second of the two circumstances that can permit departure from the placebo rule is relatively uncontroversial, and very few people who have objected to placebo-controlled studies are likely to reject this condition. The so-called clarification was flawed on three separate counts: first, it provided no criteria for the “compelling reasons” that could justify departure from the principle; second, the requirement for scientifically sound methodology is redundant, as it is required in every study and stated elsewhere in the Declaration of Helsinki; and third, it allowed participants in research to be subject to predictable serious or irreversible harm. In the following year, the clarification was elevated to the status of an amendment to the Declaration, where it remained until the recent revision in 2008.

With the change of one small word—replacing an ‘or’ with an ‘and’—the new Paragraph 32 eliminates the worst feature of the previous Paragraph 29. The new Paragraph 32 now says:

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 (italics added).

Although the condition that refers to “compelling and scientifically sound methodological reasons” remains, without further elucidation, the replacement of “or” by “and” eliminates the possibility that the design of a clinical trial with a placebo control would be ethically acceptable even if it were to subject participants to serious or irreversible harm. This change in one small word is the most salutary feature of the newly revised DoH.

Another change for the better is the addition, for the first time, of a requirement that sponsors register clinical trials: “Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.” (Paragraph 19) The virtue of this requirement is that it makes transparent just which clinical trials fail to reach a successful conclusion, either because of demonstrated lack of safety or absence of efficacy. According to one commentator, “The new proposal calling for registration of clinical trials is not likely to be followed by industry.”⁽⁹⁾ The Biotechnology Industry Organization in Washington, DC, expressed the concern that “registration of all trials might jeopardize intellectual property rights and frustrate R&D efforts while providing little guidance to prescribers and patients.”⁽⁹⁾ But it is not at all clear why registration could jeopardise intellectual property rights. Proprietary information would not be included in the registration process, and that is the only element that could, realistically, jeopardise intellectual property rights. However, if companies had to disclose a phase I trial at the outset, it might affect decisions by competitors contemplating similar trials of their own products.

Another US industry trade group, The Pharmaceutical Research and Manufacturers of America (PhRMA), also objected to the registration provision in the new DoH. PhRMA said the requirement could cause delay in mounting clinical trials, and also noted that it would impose a major burden on sponsors. What is the burden that the pharmaceutical industry is worried about? If registration would, in fact, cause such a delay in initiating the trial, the company would experience a delay in realising profits from any product that proves to be successful following phase III trials. One defender of the requirement said that a benefit would be to prevent research participants from having to go through repeated testing of the same intervention⁽⁹⁾. It appears, then, that this pits the need to protect human participants of research against the interest of industry seeking to realise financial profits as quickly as possible.

Other changes in the DoH appear to be slight changes in wording, but they have ethical implications. One example is that of providing post-trial benefits to participants. Compare the previous version to the new one. The 2000 version says, in Paragraph 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.” The new version says: “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” (paragraph 33). Are the ethical implications of the new version stronger or weaker than those of the earlier version? It’s hard to tell. The 2000 version does not mention informing participants about the outcome of the study, so that is a plus for the new version. In addition, the earlier version says that participants should be “assured of access” to methods identified by the study. But “assuring” people that they will have access is not at all the same as “ensuring access” to such methods. Nevertheless, it is possible to read the earlier version as promising more to participants than the 2008 version. The latter cites access to interventions only as “an example” of benefits resulting from the study. There may be “other appropriate care or benefits,” according to the new DoH. But what might they be? And how to determine what are appropriate care or benefits? Interpretation of these paragraphs of the DoH are left to whatever bodies, be they research ethics committees or sponsors, seek to implement the provisions of the Declaration.

Another change in the revised DoH is clearly more restrictive than the earlier version. Paragraph 19 in the 2000 version said: “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.” In the 2008 version, Paragraph 17 says: “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" (italics added). Why does this justification not apply to research for all populations, but only to disadvantaged or vulnerable populations?

Other changes in the revised DoH are mostly minor modifications of the wording in the earlier version. Overall, however, the document is stylistically inelegant. It contains redundancies, as in Paragraph 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"; and Paragraph 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." Why is Paragraph 23 necessary? Another redundancy occurs in Paragraph 33 (discussed above) and Paragraph 14, part of which says: "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." It is true that Paragraph 14 states what should be in the research protocol and Paragraph 33 addresses what the research participants are entitled to receive. Nevertheless, a better crafted document could have eliminated such redundancies and presented the items in a more logical and coherent manner.

Only time will tell whether the WMA will decide to undertake a subsequent revision of the Declaration of Helsinki, and what might prompt such a decision. For now, the Association has appointed a new working group to continue to study the matter of placebo-controlled trials.

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Workshops on biostatistics and research ethics

SGPGI will be organising workshops on biostatistics and research ethics between July and September 2009 at Lucknow. Travel support may be available.

Those interested in further details may please contact Dr Rakesh Aggarwal at the Department of Gastroenterology, SGPGI, Lucknow at sgpgi.course@gmail.com