



## Changes to the World Medical Association's Declaration of Helsinki

by Keith Dawes

Since its inception in 1964 the World Medical Association's (WMA) Declaration of Helsinki has become one of the cornerstones of medical research, providing the standard for ethical conduct of human clinical trials. Every medical writer, especially those writing protocols and informed consent forms, should have a sound knowledge of its principles particularly as the declaration has been adopted by, or influenced many national or regional legislation and regulations.

To date the declaration has undergone six revisions and two clarifications. The latest was in October 2008, where significant changes were made including further clarification on the use of placebos in clinical trials. This is arguably the most controversial aspect of the declaration and there has been significant debate on the restrictions implied by the declaration for placebos. More recently—which could eventually lead to a weakening of the declarations position—the Food and Drug Administration ruled that for clinical trials performed outside the US the International Conference on Harmonisation Good Clinical Practice guidelines can be followed and not the declaration [1]. It will be interesting to see how the declaration evolves following this decision. Controversies aside some key changes made in October are noteworthy for medical writers and these are presented below. Further reading and the full declaration can be found here <http://www.wma.net/e/index.htm>

The old declaration (from 2004) had 32 paragraphs and 2 notes for clarification; for the 2008 version there are now 35 paragraphs and no notes. New paragraphs—given verbatim except for my comments in italics—are:

- Paragraph 2: Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects *[which means you and me!]* to adopt these principles.
  - Paragraph 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 *[this represents additional protection for these vulnerable subjects]*.
  - Paragraph 19: Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject *[this is a new requirement and is likely to add further delays to setting up trials]*.
  - Paragraph 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 *[in some circumstances—such as the use of identifiable stored tissue—special permission is now required for research]*.
- The old paragraph 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' has been deleted.
- Some rewording has also occurred in many other paragraphs, but amongst others key changes are:
- Paragraph 14 now includes the following requirement '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' *[this means arrangements for aftercare need to be described in the protocol—for investigational products statements such as 'no post-trial access will be provided' are compatible with this requirement, but the subjects access to other appropriate care should be described; see also paragraph 33 in the new declaration. Provision of aftercare can also be covered by simple statements such as 'following completion of the study all subjects will be given access to appropriate treatment according to normal clinical practice'; however for certain indications and in regions where the latest medications/comparators are not always available the provision of effective aftercare may need to be guaranteed by the Sponsor—potentially a significant financial burden for drug developers]*.
  - Paragraph 15 now includes a specific statement that 'No change to the protocol may be made without consideration and approval by the *[ethics]* committee' *[this is a strengthening of the old paragraph]*.
  - Paragraph 24 which deals with provision of information to subjects now indicates that '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'. Additionally paragraphs 27 to 29 now contain further guidance on inclusion and the procedures for obtaining informed consent in subjects who

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- > are deemed incompetent or who are physically or mentally incapable of giving consent (for example unconscious subjects) *[these changes represent a strengthening of the old paragraphs, but with specific implications for how informed consent is obtained]*.
- Paragraph 30 now indicates that editors as well as authors and publishers all have ethical obligations with regard to the publication of the results of research. In addition it now states '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' *[these two key changes make editors responsible for ensuring ethical*

## Commentary on 'Changes to the World Medical Association's Declaration of Helsinki'

It is worth noting that the International Conference on Harmonisation Good Clinical Practice guidelines (ICH GCP) actually refer to the Declaration of Helsinki, which, when I was involved in drafting them, the principles involved we very much supported. Additionally, the paradox which has been created by the FDA decision to follow the ICH guidelines is compounded by the European Clinical Trials Directive, and the UK legislation that incorporates it, specifically referring to the 1996 version of the Declaration of Helsinki. By and large, however, the latest revision strongly endorses the need for patients to be protected as comprehensively as possible without putting an excessive burden on the sponsors of clinical trials to provide that protection.

The requirement to register every clinical trial in a publicly accessible database should not, in practice, be a delaying tactic. All the clinical trial applications that I have seen recently, as a member of a research ethics committee, have already been registered on, for example, [www.clinicaltrials.gov](http://www.clinicaltrials.gov). Tissue banks have benefited from the requirement to have all research projects involving the use of such tissue approved by a research ethics committee (because there is then reassurance that tissue samples will only be used appropriately). Clearly the World Medical Association has done its best to sort out the controversy over the use of placebos and the current version is probably as acceptable to all interested parties as we are likely to get. Finally, the recognition in the Declaration that editors have ethical obligations with regard to the publication of the results of research is much to be welcomed, as just possibly some interesting negative results will begin to appear.

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*publications and authors accountable for research published in their name]*.

- Paragraph 31 now provides further guidance on combining medical research with medical care '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' *[this is a strengthening of the old paragraph—but it places potential restrictions on researchers identifying suitable subjects for trials]*.
- Paragraph 32 which covers placebos has been altered '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 proven current method 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 additional risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option'.

*[This is still a very strong restriction against the use of placebos, but the second exception may allow some flexibility as 'abuse' can be interpreted in a number of ways (perhaps to allow for one placebo-controlled trial in a large clinical development programme?). Importantly, the rationale for performing a placebo-controlled trial should be clearly described in the protocol in context with these restrictions]*.

- Finally, paragraph 34 now contains an explicit statement that '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' *[again a strengthening of the old paragraph, specifically for withdrawals]*.

Altogether the changes represent a major revision of the declaration which needs to be read very carefully. It seems likely that restrictions on the use of placebos, the potential for aftercare and to register trials will all be controversial and potentially viewed as restrictive by drug developers. The wider issue for physicians is that the declaration is morally binding, and this obligation overrides national or local laws or regulations or the wishes of a clinical trial Sponsor.

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### Reference:

1. Michael D E Goodyear, Trudo Lemmens, Dominique Sprumont, and Godfrey Tangwa. Does the FDA have the authority to trump the Declaration of Helsinki? *BMJ* 2009;338:b1559, doi: 10.1136/bmj.b1559 (Published 21 April 2009).