The International Response to Helsinki VI – The WMA's Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, as adopted by the 52nd WMA General Assembly, Edinburgh, October 2000.

This brief paper summarizes some of the key comments on the Declaration as a whole or on specific provisions of the Declaration. These are not listed in chronological order.

1. In the Secretary-General's report to the 159th Session of the WMA Council, held in Divonne in May 2001, it was stressed that the overall reaction to the revised version had been extremely positive. He acknowledged that there had been criticisms of certain provisions, notably those of paras. 29 and 30.

2. An overall assessment has been given by Povl Riis, writing in *JAMA* on 20 December 2000. Riis was one of the key experts involved in drafting of the Tokyo revision (Helsinki II) in 1975. His critical comments include observations on the use of the term "other scientists", on the interpretation of "benefit", and on the non-inclusion of research on anonymized information. He considers that the need to "preserve the accuracy of the results" is part of what he refers to as a broader problem complex, including such issues as fabrication and plagiarism.

3. Another general assessment, accompanied by detailed observations on particular provisions, is given by J.L. Manzini, writing (in Spanish) in a Pan American Health Organization publication, *Acta Bioethica* (2000, Vol. 6, N° 2). He considers that all of the amendments strengthen the Declaration, and in particular assure enhanced respect for the human rights of research subjects.

4. Schuklenk's analysis of the Edinburgh revisions, published in an Indian journal, states that the WMA did not allow itself to be pressured into "lowering standards of clinical care during (author's emphasis) clinical trials" but that the WMA had ignored the problems that preventive vaccine trials will cause. He affirms that the "standard of current research ethics", as set by the Edinburgh revision, is better than was expected.

5. The Editor of the *Bulletin of Medical Ethics* has written an editorial in the journal (October 2000) which gives a very positive assessment of Helsinki VI. Noting that only 3 of the 32 paragraphs are unchanged and that 8 are entirely new, he (Richard Nicholson) affirms that the text is now the nearest it has ever been to the Nuremberg Code and the International Covenant on Civil and Political Rights (Article 7 of which deals with research on human subjects). He likewise affirms that the changes which have been introduced have a "solid ethical basis" and that if the new version "commands the wide international acceptance of previous versions… it will alter the climate in which most medical research is carried out, and may lead to some radical reassessment of what research is worth doing at all". Elsewhere in the same issue, Nicholson provides a description of all the changes and additions introduced by the new version.

6. In March 2001, a Conference, of which the WMA was one of the sponsors, was held in Pretoria on the new version of the Declaration. The concluding statement, in the March 2001 issue of *the Bulletin of Medical Ethics*, indicates that the participants acknowledged the need for further guidance to be provided on the application of the

Declaration. It was affirmed that specific issues required further discussion, "such as the use of placebos in biomedical research and the availability to persons and communities of the products of research".

7. The same issue of the *Bulletin* carries the text of a statement on the Declaration, delivered by the Director of the Office of Human Research Protections of the US Department of Health and Human Services. Indicating that the Department had not yet developed or adopted specific policy positions on the contentious issues, the statement contains three sections. The first, relating to para. 29 of the Declaration, discusses the issue of control groups in clinical trials. The second, relating to para. 30, discusses post-trial assurance of best proven therapy as identified in a trial. The third argues that the Declaration is not applicable to the full spectrum of human research, commenting that the new version of the Declaration is "by intention narrowly focused on clinical medical research".

8. In a paper published in the 12 July 2001 issue of the *NEJM*, Shapiro and Meslin agree that the new version's standard for the control group should be the "presumptive standard for trial design". Nevertheless, they argue that ethics review committees should be able to approve a deviation from this standard, but only if it is required "in order to address an urgent health problem in the host country". Further arguments against the provisions of paras. 29 and 30 are advanced in a paper by Koski and Nightingale in the same issue of the *NEJM*. They further assert that the Declaration "provides no commentary on its stated principles, making their interpretation difficult".

9. In an Editorial in the *BMJ* on 31 March 2001, Singer and Benatar affirm that the revision of Helsinki (and revisions of other research ethics codes) are "unlikely to make research more ethical around the world without some means of strengthening capacity to promote and implement such standards". They also refer to the controversy aroused by the provisions of para. 30 and comment on Bloom's advocacy of a standard of "highest attainable" (rather than "best proven") care and their own "expanded concept of the standard of care in research" (published in the *BMJ* in 2000 (Vol. 321, pp. 824-826).

10. A discursive commentary on the initial responses to Helsinki VI, focusing particularly on the placebo issue, has been published by Enserink in the 1 November 2000 issue of *Science*. This quotes some of the principal protagonists in the ongoing debate, including the Secretary General of the WMA.

11. The Editor of *IRB: Ethics & Human Research* presents (in the July-August 2001 issue) the findings of the US National Bioethics Advisory Commission and her introductory statement is followed by the NBAC's views as to what constitute "Essential Requirements for the Ethical Conduct of Clinical Trials." Some of these requirements address currently contentious issues in Helsinki VI.

12. In a letter to the *BMJ* published in the 3 February 2001 issue, Lilford and Djulbegovic express the view that the Declaration should be amended to state clearly that equipoise ("the uncertainty principle") is an essential ingredient of an ethical experiment and that the Declaration should be amended to say so. In the same issue, Rothman and Michael indicate that they would welcome any mention of an equipoise requirement in the Declaration, while in another letter Schuklenk expresses the view that there is a "clear

fault line" between the US and UK medical associations – stated to support lower standards of care for people living in developing countries – and continental European, Latin American, and some Asian medical associations – stated to reject such a double standard.

13. In a 2000 paper published in the *Medical Journal of Australia*, now somewhat dated, Stockhausen echoes a suggestion made during the September 1999 Workshop held in London on the revision of Helsinki that guidance on such issues as informed consent could be addressed in commentaries accompanying the Declaration.

14. The May-June 2001 issue of the *Hastings Center Report* contains a paper by Weijer and Anderson summarizing what they describe as the "sometimes vitriolic debate centering on the use of placebo controls", focusing on para. 29 of Helsinki VI.

15. In a paper in the 20 December 2000 issue of *JAMA*, Vastag summarizes the early responses to Helsinki VI, notably those of the FDA and the DHSS's Office for Human Research Protections, as well as comments by Nancy Dickey and Peter Lurie, Gillian Woolett (PhRMA), Thomas Quinn, Delon Human, etc. The focus of the comments is on the use of placebos and standard of care (i.e. paras. 29 and 30 of Helsinki VI).

16. Reference should be made to the EMEA/CPMP Position Statement on the Use of Placebo in Clinical Trials With Regard to the Revised Declaration of Helsinki issued in London as Document EMEA/17424/01 on 28 June 2001 (Annex 6 to Document CPMP/2020/01, dated 26 June 2001). The 2-page Statement recalls existing EU legislation on clinical trials. It points out that "although the efficacy of some new medicinal products can be satisfactorily demonstrated without the use of a placebo remains essential to demonstrate their value." The Statement enumerates "a number of conditions that govern and restrict the use of placebos in order to avoid unethical use." The final sentence of the Statements reads as follows: "Provided that the conditions that ensure the ethical nature of placebo-controlled trials are clearly understood and implemented, it is the position of the CPMP and the EMEA that continued availability of placebo-controlled trials is necessary to satisfy public health needs."

17. In an Editorial in the *Bulletin of the World Health Organization* (2001, Vol. 79, N° 4), J.E. Idänpään-Heikkilä discusses certain issues raised by the 2000 revision of the Declaration, and in particular paras. 19, 29 and 30. He affirms that "Apparently the most contentious issue in the revision of the Declaration was the role of the placebo." The revised Declaration, both on the points discussed in the Editorial and on other points, has stimulated lively debate. Capacity building for ethical and scientific review is, in his view, currently a major priority.

18. One of the most thorough (and critical) assessments of Helsinki VI is made by Forster, Emanuel and Grady in the 27 October 2001 issue of *The Lancet*. The title of their paper is "The 2000 revision of the Declaration of Helsinki: a step forward or more confusion?" The paper is lengthy, thoroughly referenced, and comprises the following sections: Process of revision; Changes to declaration; Modification of structure; Improvements, Concerns; Placebo controls; and Implementation of declaration. There are three tables (referred to as "Panels"), viz. 1. Selected major changes in wording to the declaration; 2. Selected potentially controversial additions to the declaration; and 3. Selected additions to the declaration that account for widely-accepted standards.

19. The Declaration is discussed in various passages of the US National Bioethics Advisory Commission's Report and Recommendations on "Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries", issued in April 2001. It is for example included in the tabular "Comparative Analysis of International Documents Addressing the Protection of Research Participants" (pp. 99-101 of Vol. I of the Report).

20. In a paper entitled "After Helsinki: unresolved issues in international research" (*Kennedy Institute of Ethics Journal*, 2001, Vol. 11, N° 1), Macklin discusses paras. 29 and 30 of the Declaration and asserts that certain of their provisions are contentious. She further asserts that the debate on the issues concerned continues and that the Declaration is silent on "other prominent controversies concerning international research". She goes on to state that "An analysis of these current controversies reveals reasons why they are not likely to be readily resolved, despite apparent agreement by opponents on overarching ethical principles."

21. There is a detailed analysis of some of the key provisions of Helsinki in Asad Jamil Raja's "The revised Helsinki Declaration: is it enough?", published in the Indian journal, *Issues in Medical Ethics* (2001, Vol. 9, N° 4) (originally published, in modified form, in the *Pakistan Journal of Medical Ethics* (2001, Vol. 4, pp 3-7). The focus is on paras. 19, 29, and 30, which are criticized as being problematic. There is a comment by Aasim Ahmad, entitled "Universality of care: a response", in the same issue. This author contends that the above-mentioned provisions are "not ambiguous" and that their "straightforward interpretation is protective of participants."

22. A paper (in Swedish) entitled "The Declaration of Helsinki makes a welcome clarification of placebo therapy", by J.E. Idänpään-Heikkilä, appears in the 26 October 2001 issue of the Finnish journal, *Suomen Lääkärilehti*.

23. A special section of the *British Medical Journal* of 14 December 2001 is devoted to the theme "What are the effects of the fifth revision of the Declaration of Helsinki?" It comprises four contributions, outlined below.

24. In a paper entitled "Fair partnerships support ethical research", S.M. Tollman claims that "despite the increasingly inclusive aspirations of the revised declaration, some of the absolute and exclusionary language could endanger research in developing countries." In discussing para. 29, he affirms that the "latest Helsinki revision may harm the interests it intends to protect." This paragraph may, he states, impose demands on local and national health systems that, without massive additional investments, simply cannot be met." Tollman also discusses paras. 13, 15, 19 and 30, drawing attention to potential difficulties in their implementation, as well as certain changes to Section A. Finally, he addresses the outcome of the October 2000 International Conference on Health Research for Development, held in Bangkok, stating that "Discussions about future revisions (of the Declaration of Helsinki: should take account of the views of the leaders of health research who met in Bangkok." He states: "If medical research in developing countries is to meet the high ideals of the Helsinki 2000 revision, long term individual and institutional scientific partnerships will need to be formed and sustained." The potential benefits of "balaned research collaborations" with developing countries are listed and discussed.

25. H. Bastian contributes a paper entitled "Gains and losses for rights of consumer and research participants." This is a rather critical contribution; a table is included which lists (1) Gains for consumer rights, and (2) Changes resulting in gains and losses. One of the most critical paragraphs reads as follows: "The declaration, and the association's claimed stewardship of ethics in the 21st century, has critical underlying weakness. It is not derived from a process including serious engagement with the people it seeks to protect; there is no accountability to anyone other than the medical profession (and perhaps the ethics industry); and there is no apparent evidence base or solidly articulated rationale for much of what is contained in it." She states that "Perhaps it is simply too much to hope for - that an organization that does not share decision making with the community should be able to lead ethical development in a more democratised world."

26. Sir Richard Doll's paper is entitled "Research will be impeded". He claims that "the guidelines recently issued by the World Medical Association seem, in some respects, to have been laid down without proper appraisal of the nature of the activities to which they are intended to apply." After discussing the diversity of medical research, he affirms that "It is … difficult to take seriously a whole series of principles that, according to the declaration, apply without distinction to all types of medical research involving human subjects, including research on identifiable human material or identifiable data." He goes on to state that "Strict application of the declaration's principles would make a wide range of clinical, biological, and epidemiological research impracticable or invalid", and cites examples to illustrate this point. He also criticizes para. 29, claiming that the WMA does not "seem to recognise the existence of data monitoring committees". He also states that he is "appalled by the distress that fully informed consent may sometimes cause in the absence of the escape clause that was present in the 1964 declaration."

27. L.J. Hirsch and H.A. Guess, of Merck Research Laboratories, contribute an article entitled "Some clauses will hinder development of new drugs and vaccines". They refer to para. 29, acknowledging that the WMA's Note of Clarification has addressed the issues raised by this paragraph. They state that paras. 27 and 30 still need clarification. The appointment of a panel of advisers to help with the continuing review of the Declaration is welcomed.