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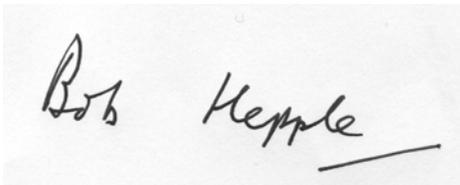
Dear Mrs Dudu

The Nuffield Council on Bioethics welcomes the opportunity to contribute to the revision of the *Declaration of Helsinki* (DoH) and is grateful to the WMA for its invitation to respond to the current consultation. I hope that our Comments at **Annex A** will be of use to the WMA's Medical Ethics Committee.

Please do not hesitate to contact us if you require clarification on any of the information provided.

Thank you again for the opportunity to respond to the consultation.

Yours sincerely



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Chairman

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Annex A

Response to the revision of the Declaration of Helsinki by the World Medical Association from the Nuffield Council on Bioethics

20 August 2007

1. The Nuffield Council on Bioethics welcomes the opportunity to contribute to the revision of the *Declaration of Helsinki* (DoH) and is grateful to the WMA for its invitation to identify paragraphs that might require revision, to propose specific amendments, and/or to propose new topics for inclusion.¹
2. The Council provides the following observations and comments for consideration by the WMA's Medical Ethics Committee and Council at the October 2007 meetings. We focus mainly on the implications of the DoH for the conduct of externally sponsored research in developing countries, a topic which the Council has considered in its publications on *The ethics of research related to healthcare in developing countries* of 2002 and 2005.² Our comments are drawn from the Council's Reports, and also take into account discussions during an international Workshop which was co-hosted by the Nuffield Council and the South African Medical Research Council, held on the same topic in Cape Town from 12-14 February 2004.³
3. We comment in particular on revisions to paragraph 12, 13, 20, 22, 29 and 30, and make observations on the general organisation of the DoH's provisions, and the need to clarify more explicitly its status.⁴

¹ See: <http://www.wma.net/e/ethicsunit/helsinki.htm>

² See: Nuffield Council on Bioethics (2002) *The Ethics of Research Related to Healthcare in Developing Countries* (London: NCOB);, Nuffield Council on Bioethics (2005) *The ethics of research related to healthcare in developing countries - a follow-up Discussion Paper* (London: NCOB), available at:

<http://www.nuffieldbioethics.org/go/ourwork/developingcountries/introduction.html>

³ See: http://www.nuffieldbioethics.org/go/ourwork/developingcountries/page_53.html

⁴ Note that commenting on the paragraphs listed here does not entail endorsement of the remaining paragraphs of the DoH. We have focused our discussion on those provisions where we consider that we have carried out sufficient research to provide robust comment.

Suggestions for revisions/amendments paragraphs that might require revision

Paragraph 12

4. Paragraph 12 reads:

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.

The Council has considered the ethics of research involving animals in a recent Report⁵ and emphasised the crucial role of the concept of the “Three Rs”. The Three Rs stand for seeking to Reduce, Refine, and Replace animal research as far as possible. The approach is desirable both to minimize ethical conflict and issues arising in relation to the transferability of results from animal studies to the human context. The Three Rs have been established in the 1950s and have become a mainstream concept in the field of animal research, acknowledged explicitly by all major funders of animal research in the UK and featuring prominently in UK law and EU policy. It would be desirable to see the Three Rs enshrined explicitly in Paragraph 12, as an appeal simply to respect animal welfare is unnecessarily vague. **We therefore propose the following addition** (addition in bold and italics):

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 ***by applying the concept of the Three Rs (Refine, Reduce, Replace)***.

Paragraph 13

5. Paragraph 13 concerns the review of research. An effective system for ethical review of research provides a crucial safeguard for research participants, especially in resource poor developing countries, as the inequalities in resources that exist between developed and developing countries pose significant risks of exploitation when externally sponsored research is carried out.

6. The structure of the review process is therefore particularly important in the context of research in developing countries, and the Council concluded in its 2002 Report that research should be reviewed in both the sponsoring country(ies) and the host country(ies) in which research takes place, to ensure the acceptability and appropriateness of crucial factors such as the standard of care to be used, or consent arrangements. Involvement of local reviewers will also help assess whether the research questions addressed match favourably with the

⁵ See: <http://www.nuffieldbioethics.org/go/ourwork/animalresearch/introduction>

research needs and priorities of the respective country. **We therefore propose to amend paragraph 13 as follows** (addition in bold and italics):

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 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. *Where the funding of a study comes from outside of the country where it is to be carried out, review should take place in both the sponsoring country(ies) and the host country(ies).*⁶

Paragraphs 20 and 22

7. Paragraphs 20-26 concern the requirement of consent. We make two observations that concern amendments which would ensure that the DoH is better suited to be used in the context of research carried out in developing countries.

Communication of information

8. The way in which information on the potential risks and benefits of research is provided is particularly important when participants are from developing countries. Those approached to participate may lack familiarity with basic practices of medical research, such as the use of clinical trials to test new treatments. Views about the causation of illness may differ from the 'western' medical model. Researchers must do their best to communicate information accurately and in an intelligible and appropriate way, taking account of local knowledge and beliefs.

Individual consent and consent by community leaders

9. When externally sponsored research is conducted in developing countries, a range of additional issues may arise when consent is sought from potential participants. For example, in some communities it is customary for male members of the family to make decisions on behalf of wives and children. There will often be a tension between the duty of

⁶ Note: references in para 13 to "the committee" (singular) should be read as references to the relevant "committees" in this case.

the researcher to be sensitive to cultural differences, and the duty to ensure that each individual has consented to participate in research.

10. **We therefore propose the following amendments** (addition in bold and italics):

20. The subjects must be volunteers and informed participants in the research project. ***In some circumstances [or: countries] it may be appropriate to approach heads of families or community leaders, but such initiatives cannot replace voluntary and informed individual consent.***

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. ***Information must be conveyed by means that are appropriate for the level of understanding of the potential subjects.*** 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.

Paragraph 29

11. Paragraph 29 reads:

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.

12. Paragraph 29 is interpreted by some to demand provision of a universal standard of care (which can be understood as the best current method of treatment available anywhere in the world for a particular disease or condition) to a control group, regardless of where the research takes place.

13. However, a number of relevant recent documents, including the *International Ethical Guidelines for Biomedical Research Involving Human Subjects* by The Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) and the *Additional Protocol to the Convention on Human Rights and Biomedicine concerning Biomedical Research*, prepared by the Steering Committee on Bioethics (CDBI) of the Council of Europe acknowledge that, in line with our own discussion on the matter, where

the “aim of research into healthcare is to improve current forms of treatment, then there may be circumstances in which it is justified to compare current local practice with a new treatment, in the local setting”.⁷

14. Thus, a non-universal standard may be acceptable for trials comparing different standards of care, where the universal standard is not available or feasible, and for investigations of preventive measures. NCOB 2002 specifies that the standard of care must be defined in consultation with those who work within the country and must be justified to the relevant research ethics committees.
15. The current version of paragraph 29 may be interpreted as preventing otherwise valuable research. **It would therefore be desirable to revise it along the following lines** (addition in bold and italics):

The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. *Where such methods cannot be made available for compelling reasons, a standard that is comparable to the level of care that would otherwise be provided in the region where research takes place should be provided.* This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

Paragraph 30

16. Paragraph 29 reads:

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.

17. The Council commented previously on paragraph 30, which concerns access to the best proven methods identified by a study⁸, with regards to:

- difficulties in relation to defining the concept of a study (as opposed to a “trial” or “research project”);
- the problem that it is unclear who should ensure post-trial access (pysicians, researchers, sponsors, policy makers); and
- the question of whether only those taking part in a study should have access, or the wider community.

The full copy of the response is at **Annex B**.

⁷ NCOB 2002, paragraph 7.30.

⁸ See: http://www.nuffieldbioethics.org/fileLibrary/pdf/WMA_para_30_NCOB_comment.pdf

18. Here we summarise that although the provision of the current paragraph 30 is commendably aspirational in concept, it may prevent valuable research in cases where it is not possible to ensure access to the best proven methods identified in a study. **We therefore recommend that the WMA reconsider the proposed revision as set out in the WMA workgroup Report of September 2003:**⁹

Before undertaking a study, the physician should make every effort to ensure that all patients entered into the study will have access to any available prophylactic, diagnostic or therapeutic method that the study proves to be the most effective and appropriate for such patients, once it has been approved by the appropriate authorities. When informing the patient about the study the physician will explain the treatment options after the study and how they relate to the patient's condition and will state explicitly if it is foreseeable or likely that the sponsors will not be able to provide effective and appropriate treatment to the patient after he or she leaves the study. Any arrangements for the continuation of treatment beyond the study, or the reasons for their absence, should be described in the study protocol (paragraph 13) that is submitted to the ethical review committee.

General comments on clarifying the status of the DoH

19. The WMA should consider using the current revision process as an opportunity to clarify the status of the DoH in the very brief statement in paragraph 1.¹⁰ One way of doing this would be by adding a preamble which sets out explicitly that "the Declaration is a set of ethical guidelines, not laws or regulations", as envisaged in a 2004 WMA workgroup report.¹¹
20. When the WMA considered a proposal for revisions to paragraph 30 at the WMA General Assembly in September 2003, 'sharp differences of opinion', led to the amendment not being adopted.¹² Instead, another

⁹ WG/DoH/Sept2003, Workgroup report on the revision of paragraph 30 of the declaration of Helsinki, http://www.wma.net/e/pdf/wg_doh_sept2003.pdf

¹⁰ "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."

¹¹ World Medical Association (2004) *Workgroup Report on the revision of paragraph 30 of the Declaration of Helsinki.*, available at: http://www.wma.net/e/ethicsunit/pdf/wg_doh_jan2004.pdf , see also: *The ethics of research related to healthcare in developing countries - a follow-up Discussion Paper* (2005) available from:

<http://www.nuffieldbioethics.org/go/ourwork/developingcountries/introduction.html#p39>

¹² World Medical Association (2003) Press release 14 Sept *WMA to continue discussion on Declaration of Helsinki*. Available:

http://www.wma.net/e/press/2003_19.htm Accessed on 3 Feb 2005

Workgroup was established to clarify the controversy. The Workgroup's Report outlined three options:

- not to revise paragraph 30, but to add preamble explaining that the Declaration is not a regulatory or legal device;
- to add a note of clarification setting out the intention of the paragraph; or
- not to make any changes and to issue a separate statement on equitable access to healthcare.¹³

21. The current consultation on the revisions of the DoH will attract comments from a wide range of stakeholders and similar difference of opinion about how to implement the proposals could arise at the WMA's General Assembly in October. Some tension could be avoided by clarifying the status of the DoH. The WMA's 2004 Workgroup Report proposed the following preamble:

As a statement of principles, the Declaration of Helsinki is intended to establish high ethical standards that guide physicians and other participants in medical research involving human subjects. These ethical principles provide the basis of moral reflection on the means and goals of research involving human subjects, distinct from national legal and regulatory requirements. Interpreting the provisions of the Declaration regarding the design, conduct or completion of the research requires careful balancing of all of the Declaration's ethical principles. Differences in interpretation should be resolved by physicians and other participants involved in the research who are most familiar with all relevant factors, including the needs of research participants and of the host population.

22. This draft, which explicitly states that the status of the DoH is distinct from law and regulation, and emphasises that its provisions require interpretation, and do not provide off-the-shelf 'solutions' to ethical problems, seems like a suitable basis for discussion.

23. Based on feedback which the Council receives on the occasion of making presentations on the findings of its reports on the ethics of research related to healthcare it appears that there is a considerable degree of confusion about the nature of the provisions of the DoH, and its status, especially among industry groups. A clarification will be helpful to ensure a better understanding of the document, and to convey the message that acting morally is not the same as simply complying with rules and regulations, but rather requires the making of complex case-sensitive judgments and explicit justification. It will be useful to draw on the DoH in this respect, but doing so is a starting,

¹³ World Medical Association (2004) *Workgroup Report on the revision of paragraph 30 of the Declaration of Helsinki.*, available at:
http://www.wma.net/e/ethicsunit/pdf/wg_doh_jan2004.pdf

rather than an endpoint. A preamble would be a helpful tool in clarifying the matter.

24. Regarding guidance on the interpretation of specific paragraphs, it might furthermore be helpful to add an explanatory report which could draw on the comments the WMA received over the years and in the current consultation on specific provisions. Many provisions are somewhat abstract and technical, and case studies which could be included in an explanatory report would be useful in illustrating the need and scope of interpretation of specific paragraphs.

Annex B

Commentary on the World Medical Association's current revision of paragraph 30 of the Declaration of Helsinki

From the Nuffield Council on Bioethics

The Nuffield Council on Bioethics welcomes the opportunity to contribute to the continuing discussion about paragraph 30 of the *Declaration of Helsinki* (DoH) and is grateful to the WMA for its invitation to submit comments on the current draft Report of its workgroup.¹

The Council provides the following observations and comments for consideration by the WMA's Medical Ethics Committee at its meeting on 13-15 May 2004. The comments are focusing particularly on the implications of paragraph 30 for the conduct of externally sponsored research in developing countries. They are drawn from the Council's Report *The ethics of research related to healthcare in developing countries*, published in April 2002. They also take into account discussions during an international Workshop which was co-hosted by the Nuffield Council and the South African Medical Research Council, held recently on the same topic in Cape Town from 12-14 February 2004.²

'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.'
Paragraph 30 DoH

The provision of the current paragraph 30 is commendably aspirational in concept. However, the Council also shares the view expressed in the WMA's most recent workgroup Report that its wording 'is not perfect'.³

We note that it was not possible for delegates of the WMA's meeting in September 2003 to agree on the proposed revision of paragraph 30, as suggested by the previous workgroup Report:⁴

¹ <http://www.wma.net/e/ethicsunit/helsinki.htm>

² The Report can be downloaded from our website at <http://www.nuffieldbioethics.org/developingcountries/index.asp>. Details about the conference can be found at http://www.nuffieldbioethics.org/developingcountries/pp_0000001268.asp.

³ WG/DoH/Jan2004, Workgroup report on the revision of paragraph 30 of the declaration of Helsinki, http://www.wma.net/e/ethicsunit/pdf/wg_doh_jan2004.pdf

'Before undertaking a study, the physician should make every effort to ensure that all patients entered into the study will have access to any available prophylactic, diagnostic or therapeutic method that the study proves to be the most effective and appropriate for such patients, once it has been approved by the appropriate authorities. When informing the patient about the study the physician will explain the treatment options after the study and how they relate to the patient's condition and will state explicitly if it is foreseeable or likely that the sponsors will not be able to provide effective and appropriate treatment to the patient after he or she leaves the study. Any arrangements for the continuation of treatment beyond the study, or the reasons for their absence, should be described in the study protocol (paragraph 13) that is submitted to the ethical review committee.'⁵

The Council realises that controversies arose because some of those discussing the possible revision of paragraph 30 perceived a conflict with 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.'

The Council makes the following observations:

The DoH is widely regarded as the pre-eminent ethical guidance on healthcare research. It is not, as such, a regulatory device or binding legislation. Nonetheless, a number of countries refer to the provisions of the DoH in their national laws and regulations governing research involving human participants. Similarly, organisations and companies sponsoring research frequently request that researchers receiving funding abide by its requirements. Therefore, at present, the DoH is not only referred to as a document which formulates aspirational ideals, but one that has very real implications for policy and practice of healthcare research.

The current phrasing of paragraph 30 is usually understood to mean that research is only justified if proven interventions will be made available to all those participating in trials, and ideally also to the wider community. In principle, this approach is to be welcomed. It is particularly relevant with respect to developing countries, especially where research leads to the development of interventions which have not been available previously.

⁴ WG/DoH/Sept2003, Workgroup report on the revision of paragraph 30 of the declaration of Helsinki, http://www.wma.net/e/pdf/wg_doh_sept2003.pdf.

⁵ WG/DoH/Sept2003, Workgroup report on the revision of paragraph 30 of the declaration of Helsinki, http://www.wma.net/e/pdf/wg_doh_sept2003.pdf.

However, our main concern with regard to making the access to newly developed treatment a *conditio sine qua non* is that it is unlikely to be feasible in practice in all cases. This is particularly true for continued treatment for chronic disease.

We are aware that it is difficult to formulate general guidance that will apply in all circumstances. However, if researchers or sponsors were required categorically to fund the future provision of interventions, either to participants in the study or to the wider community, many are likely to cease to support the research. In particular, sponsors from the public sector are likely to be unable to bear the costs involved without curtailing other research. It is crucially important that opportunities to improve healthcare, and to undertake otherwise beneficial research, should not be lost. The costs of 'doing nothing' can be considerable, especially for people in developing countries.

The Council therefore emphasises the importance of addressing the difficult questions raised by externally sponsored clinical trials at the planning stage. Negotiations during the study, or at its end can lead to undesirable tensions and delays in making available proven interventions. Researchers should therefore endeavour, before the start of a trial, to secure post-trial access for effective interventions for all participants, and, ideally, for the wider community. In determining whether, and if so, for how long researchers or sponsors should provide treatment, it is important to assess their own capacity as well as that of the national health care system. It is therefore important to be proactive in liaising with relevant government departments. The lack of provision of continued treatment either through the sponsor or the relevant national healthcare system should be justified to research ethics committees, in the sponsoring country as well as in the country where the research takes place (see paragraph 9.31 of our Report). **In principle, we see this approach reflected in the suggested revision of paragraph 30 proposed in the WMA workgroup Report of September 2003. We therefore recommend that the WMA reconsider the proposed text to replace the current paragraph 30.**

However, we also make the following further observations with regard to the final wording of a possible revision of paragraph 30, as suggested by WMA's workgroup in September 2003:

- Only rarely does a single research study lead to the discovery of a new intervention that can be introduced promptly into routine care. Phase I trials have different objectives, and results of most epidemiological and observational studies do not usually translate into new medical interventions, (see paragraph 9.34 of our Report). Hence, it may not

be meaningful to require the accessibility of post-trial treatment for all studies. Also, it is not always straightforward to determine when a study, a trial or a research project is completed. These issues should be clarified.

- It is clear that the DoH is directed primarily to physicians. The draft paragraph 30 provides: that physicians should make every effort to ensure that all patients entered into the study will have access to any available ... therapeutic method' This wording is problematic.
 - First, in view of the professional competency and capacities of physicians and in view of the practical constraints affecting the planning of research, particularly in developing countries, it is unlikely that they can make 'every effort to ensure' availability of proven interventions. We suggest that those involved should rather be asked to make 'appropriate efforts'.
 - Secondly, the wording seems to suggest that the obligation to ensure provision of continued treatment is with the physician alone. This ignores the complexity of the issue of ensuring post-trial treatment. Decisions are made by number of stakeholders, and it would be more appropriate to acknowledge the complex interplay among sponsors, local governments and the physicians conducting the research. This should be reflected in a possible revision of paragraph 30.
- The exploration of making accessible post trial treatment should not only be restricted to those taking part in the trial. Consideration should also be given as to whether treatment can be made available to the community from whom trial participants have been recruited. Provision of treatment to the wider community is especially relevant in the case of vaccine trials. The main purpose of conducting clinical trials is to evaluate interventions that may be applied in the wider community, of which the participants in the trial are but a sample. Researchers and sponsors must be aware of this guiding principle and justify their decision carefully, should for example, economic considerations make it difficult to make available a proven intervention, if they wish to avoid the charge of exploitation (see paragraph 9.3 of our Report).
- Requiring that new interventions should be made available 'once it has been approved by the appropriate authorities' may not always be a practical requirement:

- Often, such requirements will imply a considerable delay in the provision of treatment. If interventions are sufficiently advanced, possibilities could be explored to provide access to treatment before full regulatory approval. This is especially important in the case of interventions regarding life-threatening or seriously debilitating conditions where alternative interventions are ineffective or unavailable;
- Concern has also been expressed that suspending the provision of treatment until regulatory approval will leave trial participants without treatment. Consequently, it has been recommended that this issue should be addressed in a revised paragraph 30.⁶

It is clear from the comments above that it is difficult to address in paragraph 30 all aspects which need to be considered in relation to post-trial access to proven interventions. Accordingly, the WMA may be reluctant to stipulate detailed requirements. Furthermore, the WMA may wish to keep the DoH as general as possible in order to preserve the original aspirational spirit of the DoH. Clearly, it would be undesirable for the DoH to be mistaken for a regulatory device.

We acknowledge that these concerns raise important issues which relate to the status and practical application of guidance documents. However, we emphasise again that it is crucial to clarify that paragraph 30 should not be understood as prohibiting research unless access to proven interventions can be guaranteed, especially with regard to the current use and influence of the DoH.

It is important that the scope of any statement relating to post trial treatment is recognised by all relevant stakeholders as balanced and reasonable. Overly idealistic provisions are not likely to enhance the perception of the DoH. Therefore, there may be merit in considering a less detailed revision of paragraph 30, along the lines of the following suggested wording:

‘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. *If this is likely to be unfeasible, the reasons for undertaking the study*

⁶ While this question has not been addressed in detail in the Council’s Report, participants of the Workshop which was held in Cape Town from 12-14 February 2004 noted that there was a risk that suspending the provision of treatment until regulatory approval would leave trial participants without treatment. This was especially relevant in the case of trials of interventions to control potentially fatal chronic conditions. It was therefore important that physicians, sponsors and local governments considered carefully how continued treatment could be provided. It was emphasised that this issue should be addressed in a revised paragraph 30.

nonetheless must be justified to relevant ethics committees and participants should be informed about the treatment options after the study before they give their consent’.

As is well known, there have been a number of controversies which arose from ambiguous provisions of guidance in the past, most notably with regard to the standard of care provided in HIV transmission trials.⁷ Some of the ensuing discussion has helped both sides in the controversy to better understand the reasons for differing interpretations. Subsequently, many agreed that neither side could be described adequately as acting ‘unethically’. While this is a desirable outcome, the Council takes the view that it is important that conflict be pre-empted. Avoiding unnecessary ambiguity of guidelines plays an important role. It can prevent damage in relation to the trust and understanding among and between investigators, regulators and sponsors. Equally, it will help to ensure that healthcare-related research in developing countries is not slowed down, delayed or inhibited altogether. **We therefore strongly recommend that the WMA’s Medical Ethics Committee disregard the conclusion of the current draft Report of its workgroup not to revise or amend paragraph 30 of the DoH.**⁸ The matter of providing post trial treatment is too important not to be addressed explicitly in the Declaration of Helsinki.

⁷ Lurie P, Wolfe SM (1997) Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries, *New England Journal of Medicine*, 337(12): 853–856; Angell M (1997) The ethics of clinical research in the third world, *New England Journal of Medicine*, 337(12): 847–49.

⁸ WG/DoH/Jan2004, Workgroup report on the revision of paragraph 30 of the declaration of Helsinki, http://www.wma.net/e/ethicsunit/pdf/wg_doh_jan2004.pdf