

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:

- o 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;
- o 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