

*DOCUMENTATION FOR THE PREPARATION OF NOTE
OF CLARIFICATION ON PARAGRAPH 30 OF THE
REVISED DECLARATION OF HELSINKI*

A. Published literature and similar sources

This paragraph lays down that at the conclusion of a study, every patient who is part of the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

The comments, etc. that follow have been derived from several sources and are not cited here in any particular order of importance or priority.

1. The following comments were made by Pharmaceutical Research and Manufacturers of America (PhRMA) in a Discussion Paper dated June 2001:

“Article 30 appears to require research sponsors to supply research participants, at the conclusion of a clinical trial, with whatever treatments were found to be best in that particular clinical trial. This raises important ethical and practical concerns, as well as the spectre of an unintended consequence – the establishment of unnecessary barriers to research and treatments for the developing world. The Declaration clearly prohibits coercing individuals to participate in research (see Article 20) – a prohibition that the research-based pharmaceutical industry fully supports. The act of guaranteeing research participants access to treatments after the conclusion of a trial could constitute undue inducement to participate. Moreover, from a scientific perspective, it is virtually impossible to identify the “best” treatments on the basis of a single study. From a legal perspective, a research sponsor could be in conflict with local laws and regulations, by promising to supply and distribute biomedical products that are not approved locally for use, or that are made and marketed by another organization (please see Appendix 2 for more details).

Sponsors of clinical trials do facilitate access to new medicines by establishing the safety and efficacy of a new drug, but it is unrealistic and misleading to suggest that they can ensure access to drugs for any given population. Only local governments, not pharmaceutical companies, can make decisions about initial, and particularly ongoing, access to new drugs. Moreover, in order to ensure the delivery and safe and effective use of ongoing health care services, including access to medicines, there is a need first to establish an appropriate infrastructure (e.g. roads, transportation, electricity, and water supplies). Such an infrastructure is not available in many parts of the developing world. Establishing and improving infrastructure requires a collective and concerted effort by international organizations, donor governments, and non-governmental organizations as well as industry.”

Elsewhere, the PhRMA has suggested new wording for para. 30, as follows:

“The information obtained from the study as well as cumulative knowledge of the method and the disease being studied, should be used as a foundation for the provision of long term access to the most appropriate prophylactic, diagnostic and therapeutic methods for the study population.”

The justification for this proposed revision is as follows:

“From a scientific and practical perspective, it is virtually impossible to identify the so-called ‘best’ treatments on the basis of a single study. From a legal perspective, a research sponsor could be in conflict with local laws and regulations by promising to supply and distribute biomedical products that are not approved locally for use, or that are made and marketed by another organization. The research results should form the basis, in conjunction with other relevant information, for the eventual local approval of a therapeutic agent appropriate for the target population. The revised text given above appropriately acknowledges that providing access to medicines is an obligation shared with Governments, NGOs, and others.”

2. A critical analysis of para. 30 was given by Greg Koski, Director of the Office for Human Research Protections, US Department of Health and Human Services, at a Conference on the

revised DoH, held in Pretoria in March 2001. It is reproduced below in full (under the heading “Post-trial assurance of best proven therapy as identified in the trial (para 30)”):

“A new section within the revised DoH, concerning the assurance that, at the conclusion of the study, the best proven intervention identified by that study be made available to every patient enrolled, has raised a number of serious concerns for government sponsors of research. The current version does not recognize the fact that there is often disagreement about what the ‘best current prophylactic, diagnostic, and therapeutic methods’ are, or that they can vary by population or geographic area. In fact, it seems to assume that the ‘best method’ can always be ascertained by a single clinical trial conducted in one geographic location, which is rarely the case. A single trial rarely can determine how best to prevent or treat a disease in all settings, even in the precise setting in which it was conducted.

Para. 30 rests on the assumption that a single clinical trial, even if ‘positive’, would provide certainty as to how best to prevent or treat a given disease. Good trials provide clinically relevant results. However, in order to weigh potential benefits against possible harms, consensus about prevention or treatment for any given condition requires the examination of the outcomes of that trial in the context of other clinical trials, as well as an effort to scrutinise information from related clinical and related basic and applied research efforts. The results of one study might not be expected to be sufficient to mobilise a change in health care delivery, but, in certain circumstances, could lay a foundation for such changes.

If ‘proven’ is taken to mean ‘approved by a regulatory body’, then a number of years might pass before the requisite data are submitted and reviewed and the data validated for reliability through site visits. Moreover, once determined to be efficacious in a controlled trial setting, additional studies will often be needed to test the effectiveness of the intervention in actual practice. Studies are also frequently needed to identify effective delivery mechanisms and ways to influence behaviours of the population to make prevention and treatment interventions accessible to the intended populations. What ‘proven’ means in the DoH context is not clear, and will likely be of little help to ethics review committees.”

3. Writing in the *British Medical Journal* on 15 December 2001 (Vol. 323, p. 1417, Laurence Hirsch and Harry Guess, of Merck Research Laboratories, affirm that the current wording of para. 30 raises concerns. They write as follows:

“Firstly, none of the methods used in the study may be found to be suitable. Secondly, a single study can rarely identify “best” treatment. This is especially true for early stage trials, including proof of concept studies and dose ranging studies. Thirdly, a new drug or device may not be approved until several years after the end of a trial. Consequently, providing as yet unapproved treatment to trial participants on completion of the study may conflict with local regulations. Finally, an offer to provide treatment that is otherwise unavailable on completion of the trial might be considered an undue inducement to potential participants.

Improvements in medical infrastructure require collaborative efforts between public and private partners; mandating that sponsors of studies provide treatment is not, by itself, the answer to this complex issue. The best way to provide treatment after a trial will vary with local conditions and infrastructure and should reflect input from local healthcare providers.”

4. Writing in the same issue of the *BMJ*, Stephen Tollman, of the University of the Witwatersrand, states that the provisions of para. 30 “would be difficult for many local health systems to fulfil.”

5. In a paper in *The Lancet* published on 27 October 2001 (Vol. 358, pp. 1449-1453), Heidi Forster, Ezekiel Emanuel, and Christine Grady (of the US National Institutes of Health) describe the provisions of para. 30 as important, commenting that “Much recent debate has stemmed from the fact that in many studies, provisions are not in place to assure participants access to products that are proven effective through their participation in the trial.” Unfortunately, they state, “how to assure access, and whose responsibility it is, are challenges left unanswered” by the 2000 version of the Declaration.

6. In an Editorial on the DoH published in the *Bulletin of the World Health Organization* (2001, Vol. 79, p. 279), Juhana Idänpään-Heikkilä, of the Council for International Organizations of Medical Sciences, states that “Some object that for a sponsor and researcher

[compliance with para. 30] could mean a costly long-term commitment, which would deter them for undertaking the research.”

7. In a paper in the *International Journal of Pharmaceutical Medicine* (2001, Vol. 15, pp. 113-114), Roger Bickerstaffe (Chairman, European Forum for Good Clinical Practice) discusses the concept of “best proven treatments” for comparators (para. 29) and for continuation therapy at the end of every study (para. 30). He states the following:

“This suggests a ready agreement about what is ‘best’, which in reality is elusive. All judgements on such matters come from balancing risks and benefits across available data. Having done that for a population or group ‘on average’, it still does not predict what a particular patient will do best on. Pharmaceutical medicine wrestles constantly with the differences between patients and their responses to therapy, so much so that the science of pharmacogenetics continues to develop rapidly. Simply striving to want to be able to give everybody ‘the best’ creates a nightmare, and it fails to respect inherent biological differences between persons, which are particularly important for the individuals.”

He has certain other comments on para. 29, not covered here.

8. A paragraph-by-paragraph analysis of much of the DoH 2000 appears in the October 2000 issue of the *Bulletin of Medical Ethics* – para. 30 is described as “potentially the most far-reaching of all the changes to the Declaration.” The analysis continues in the following terms:

“Inserted primarily to prevent abuse of third world populations by researchers who ‘parachute’ in, do a study, and then depart leaving no improvement in health care for that population, its implications are wider. Given that it is known in advance that many therapies resulting from advanced genetic or biotech work will be very expensive, there is always the risk that health authorities in rich countries will opt not to pay for them. Trial sponsors doing research in any country may soon find that they have to give a cast iron guarantee that, if successful, the study drug will be provided for as long as needed to the trial subjects.”

9. In a paper in the *Kennedy Institute of Ethics Journal* (2001, Vol. 11, pp. 17-36), Ruth Macklin (Albert Einstein College of Medicine, New York) describes para. 30 as a “close runner-up for contentiousness” to para. 29 in the revised version of the DoH. She analyses the issues raised by those (and other) paragraphs.

10. A paper by Asad Jamil Raja (Department of Surgery, Aga Khan University, Karachi) on the revised DoH appears in the *Indian journal Issues in Medical Ethics* (2001, Vol. 9, pp. 114-116); it was originally published in the *Pakistan Journal of Medical Ethics* (2001, Vol. 4, pp. 3-7). The author asserts that para. 30 requires many clarifications:

“What does one understand by ‘assured access’? Is it free access? For how long? If an antihypertensive drug is tested, should participants receive free access to the drugs life long? What precisely does one owe the community once research is over?

Is one trial enough to prove that it is the best therapy? How many more trials are necessary before it should become practice? The results of one study might not be sufficient to justify a change in practice, but it may in some cases lay the foundation for such changes. After the conclusion of a successful phase II trial of a drug it could take another four to six years before regulatory bodies approve this drug as a proven treatment. Before that, it is all research. How does one interpret this clause in the context of a community which is undergoing a Phase II trial? Also, consider the logistics and financial constraints to adopting a new treatment or intervention on a population-wide basis. At times they may be almost insurmountable. This again raises questions which have no obvious answers.” (A footnote has been omitted)

11. In an accompanying contribution to the same Indian journal (*ibid.*, p. 117), Aasim Ahmad (Department of Medicine, Aga Khan University, Karachi) takes issue with points made in the above paper. He affirms that, to him, “it is clear that assured access means exactly that: if a person cannot afford the treatment, it should be provided free. If treatment is to be given life long, then life long it is.”

12. In an editorial in the *British Medical Journal* issue of 31 March 2001, Peter A. Singer and Solomon Benatar refer to the controversy aroused by the provisions of para. 30 and comment on Barry 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).

13. In the course of a Consultation convened by the WMA in Divonne-les-Bains on 8 September 2001, Dr Tom Gallacher (representing the IFPMA) stated that the industry had concerns over the current wording of para. 30, viz.:

- “- a single trial does not provide definitive proof of ‘best proven therapy’;
- registration is not always assured due to regulatory barriers peculiar to certain countries;
- healthcare provision is not a responsibility of the research sponsor;
- [the present text] could prove a disincentive for industrial R&D, particularly for neglected diseases.”

14. The concerns of one research-based pharmaceutical company (Schering-Plough) in respect to para. 30 were formulated at the same Consultation by Jean-Louis Saillet (Schering-Plough Research Institute).

15. At a meeting of a WMA Workgroup on the DoH held on the following day (9 September 2001), it was agreed that para. 30 was “probably unrealistic in its expectation of researchers and sponsors of research [and] should be changed to provide a more balanced view on the requirements of ethical research.”

16. Certain criticisms of para. 30, in the context of preventive vaccine trials (e.g. HIV vaccine trials), are made by Udo Schüklenk, of the University of the Witwatersrand, in a paper in the Indian journal *Issues in Medical Ethics* (2001, Vol. 9, p. 29).

17. A section entitled “Post-trial benefits” is included in a paper by Harold Shapiro and Eric Meslin (who served as President and Executive Director respectively of the now-dissolved US National Bioethics Advisory Commission), published in the *New England Journal of Medicine* (2001, Vol. 345, pp. 139-141). The following are extracts from this section:

“Making a successful new intervention available to participants after a trial is an especially important ethical obligation. There is a related obligation to ensure that

participants are no worse off during the trial than they were before it. In addition, we believe that research participants should not be made worse off as a result of their inability to have continued access to the successful intervention after the trial has ended. Although the researcher – participant relationship is different from the doctor – patient relationship, trust in the medical profession is central to anyone’s willingness to participate in a trial. Any sense of abandonment is difficult to address adequately in the informed-consent process.

A plan for the routine provision of a successful new intervention to participants after a trial has been completed is one way to ensure that the study is responsive to the health needs of the host country. The ethical obligation to provide the intervention to others in the community who might benefit from it is considerably less strong, but a plan to do so would help reduce the risk of exploitation.”

18. A paper by Brian Vastag entitled “Helsinki discord? A controversial Declaration” appeared in the 20 December 2000 issue of the *Journal of the American Medical Association* (Vol. 284, No. 23). Gillian Woollett of the PhRMA is quoted in respect to para. 30. She points out that supplies of drugs provided to study participants after a trial “could be expensive for drug makers.” The following is a relevant extract from Vastag’s article:

“Paragraph 30 of the revision addresses this issue [i.e. post-trial provision of drugs to study participants], stating that all participants in a clinical trial should have access to the best therapy after the study. Making drug companies bear this burden could slow new trials, argues Woollett. Asking the governments of developing nations to pay for the treatments is another option, but developing nations generally spend woefully few dollars on health care as it is.”

B. INTERNATIONAL TEXTS ON THE ETHICAL CONDUCT OF MEDICAL RESEARCH

1. 2002 Revision of CIOMS Guidelines (provisional version of 29 June 2002)

Guideline 21 and the first two paragraphs of the commentary read as follows:

“Guideline 21: Ethical obligation of external sponsors to provide health-care services

External sponsors are ethically obliged to ensure the availability of:

- **health-care services that are essential to the safe conduct of the research**
- **treatment for subjects who suffer injury as a consequence of research interventions**
- **services that are a necessary part of the commitment of a sponsor to make a beneficial intervention or product developed as a result of the research reasonably available to the population or community concerned.**

Commentary on Guideline 21

Obligations of external sponsors to provide health-care services will vary with the circumstances of particular studies and the needs of host countries. The sponsors’ obligations in particular studies should be clarified before the research is begun. The research protocol should specify what health-care services will be made available, during and after the research, to the subjects themselves, to the community from which the subjects are drawn, or to the host country, and for how long. The details of these arrangements should be agreed by the sponsor, officials of the host country, other interested parties, and, when appropriate, the community from which subjects are to be drawn. The agreed-upon arrangements should be specified in the consent process and document.

Although sponsors are, in general, not obliged to provide health-care services beyond that which is necessary for the conduct of the research, it is morally praiseworthy to do so. Such services typically include treatment for diseases contacted in the course of the study. It might, for example, be agreed to treat cases of an infectious disease contracted during a trial of a vaccine designed to provide immunity to that disease, or to provide treatment of incidental conditions unrelated to the study.”

2. *UNAIDS Guidance Document on “Ethical Considerations in HIV Preventive Vaccine Research” (May 2000)*

Guidance Point 2 (Vaccine availability) reads as follows:

“Any HIV preventive vaccine demonstrated to be safe and effective, as well as other knowledge and benefits resulting from HIV vaccine research, should be made available as soon as possible to all participants in the trials in which it was tested, as well as to other populations at high risk of HIV infection. Plans should be developed at the initial stages of HIV vaccine development to ensure such availability.”

The commentary of this Guidance Point is not reproduced here

Guidance Point 16 (Care and treatment) reads as follows:

“Care and treatment for HIV/AIDS and its associated complications should be provided to participants in HIV preventive vaccine trials, with the ideal being to provide the best proven therapy, and the minimum to provide the highest level of care attainable in the host country in light of the circumstances listed below. A comprehensive care package should be agreed upon through a host/community/sponsor dialogue which reaches consensus prior to initiation of a trial, taking into consideration the following:

level of care and treatment available in the sponsor country

highest level of care available in the host country

highest level of treatment available in the host country, including the availability of antiretroviral therapy outside the research context in the host country

availability of infrastructure to provide care and treatment in the context of research

potential duration and sustainability of care and treatment for the trial participant.”

The lengthy commentary on this Guidance Point is not reproduced here.

3. *WHO Guidelines for GCP for Trials on Pharmaceutical Products (1995)*

Item 23 of Appendix 2 (Model list of items to be included in a clinical trial protocol) reads as follows:

“Medical care to be provided after the trial, and modalities of post-trial treatment.”

4. *ICH Harmonised Tripartite Guideline for GCP (1996)*

No directly relevant provisions were identified, except for para. 4.3.2 which deals with post-trial care if adverse events occur during the trial.

5. *Council of Europe Draft Additional Protocol on Biomedical Research (April 2002 version)*

No directly relevant provisions were identified.

6. *EU Directive 2001/20/EC of the European Parliament and of the Council on GCP for clinical trials (4 April 2001)*

No directly relevant provisions were identified.

C. RECENT REPORTS ON ETHICAL ISSUES IN CLINICAL TRIALS, ETC. IN DEVELOPING COUNTRIES

There is a lengthy discussion of “Access to post-trial benefits” in the Executive Summary of the US National Bioethics Advisory Commission’s April 2001 Report on “Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries.” The subsequent Recommendation reads as follows:

“*Recommendation 4.1:* Researchers and sponsors in clinical trials should make reasonable, good faith efforts before the initiation of a trial to secure, at its conclusion,

continued access for all participants to needed experimental interventions that have been proven effective for the participants. Although the details of the arrangements will depend on a number of factors (including but not limited to the results of a trial), research protocols should typically describe the duration, extent, and financing of such continued access. When no arrangements have been negotiated, the researcher should justify to the ethics review committee why this is the case."

There is also a discussion, under the heading "Providing benefits to others", about the "justice of differentiating between former trial participants and others in the host community who need similar medical treatments." Although the recommendations go beyond the limits of the language of para. 30, they are reproduced here because of their potential interest to readers of this paper:

Recommendation 4.2: Research proposals submitted to ethics review committees should include an explanation of how new interventions that are proven to be effective from the research will become available to some or all of the host country population beyond the research participants themselves. Where applicable, the investigator should describe any pre-research negotiations among sponsors, host country officials, and other appropriate parties aimed at making such interventions available. In cases in which investigators do not believe that successful interventions will become available to the host country population, they should explain to the relevant ethics review committee(s) why the research is nonetheless responsive to the health needs of the country and presents a reasonable risk/benefit ratio.

Recommendation 4.3: Whenever possible, preceding the start of research, agreements should be negotiated by the relevant parties to make the effective intervention or other research benefits available to the host country after the study is completed."

An entire Chapter (9) of the May 2002 Report of the London-based Nuffield Council on Bioethics on "The Ethics of Research Related to Healthcare in Developing Countries" is devoted to the theme "What happens once research is over?" The question of post-trial access to interventions and products shown to be effective is dealt with in several places in the Report; the following are among the most salient conclusions and recommendations:

10.44 With regard to the provision of an intervention shown to be successful once the research is completed, there are three groups of people to be considered: members of the control group in a trial, all of the participants in the research project, and the wider community in which the research took place.

10.45 We conclude moreover that it would not be ethically acceptable for any study to begin without a decision having been made about whether or not those in control groups will be offered an intervention shown to be successful on completion of the trial, where relevant and appropriate. Participants should be informed of the decision as part of the process of obtaining their consent (paragraph 9.27).

10.46 We therefore endorse the US National Bioethics Advisory Commission (NBAC) recommendation that researchers should endeavour before the initiation of a trial to secure post-trial access for effective interventions for participants in the trial and that the lack of such arrangements should have to be justified to a research ethics committee (paragraph 9.31).

10.48 We recommend that the following issues are clearly considered by researchers, sponsors, national healthcare authorities, international agencies and research ethics committees as part of any research protocol before research relating to healthcare involving the testing of new interventions is undertaken:

- the need, where appropriate, to monitor possible long-term deleterious outcomes arising from the research, for an agreed period of time beyond the completion of the research
- the possibility of providing participants with the intervention shown to be best (if they are still able to benefit from it), for an agreed period of time
- the possibility of introducing and maintaining the availability to the wider community of treatment shown to be successful (paragraph 9.48).

10.48 We endorse the NBAC recommendation that research proposals submitted to those committees should include an explanation of how new proven interventions could be made

available to some or all of the host country population and that investigators should justify to the relevant research ethics committee why the research should be carried out if this is not thought possible (paragraph 9.49). (Footnotes have been omitted)

The paragraph numbers cited refer to the corresponding paragraphs in the body of the Report.

D. NATIONAL LEGISLATION AND GUIDELINES

The US Report referred to above includes, in Vol. 11, a “Comparative analysis of international documents addressing the protection of research participants.” One of the points analysed is the “Duty owed to research participants during/after trial.” Information is provided on relevant provisions in the following countries: Australia; Brazil; Canada; China; Finland; France; India; the Netherlands; New Zealand; South Africa; Thailand; Uganda; United Kingdom; USA.

The UK Report referred to above includes a Table 5 (Examples of national guidance on what should be provided once research is over) in Appendix 1 (Guidance on research related to healthcare). Information is provided on relevant provisions in the following countries: Brazil; India; South Africa; Uganda; the United Kingdom. The tabular information *re* the UK does not cover the Medical Research Council’s July 1998 Interim Guidelines on Research Involving Human Participants in Developing Societies: Ethical Guidelines for MRC-sponsored Studies. These include the following Specific Consideration 9:

“In anticipation of any beneficial results of therapeutic research, there should normally be discussion in advance with relevant parties in the developing society about the dissemination of those results to study participants and local inhabitants, and about subsequent availability of the relevant product to local inhabitants.”

