

Ethical principles for the guidance of physicians in medical research — the Declaration of Helsinki

Juhana E. Idänpään-Heikkilä¹

Advances in medicine depend on innovative and bold clinical research. Much of the progress we have seen in the effectiveness and safety of disease treatment, diagnosis and prevention is the result of intensive research involving human subjects. This research has undoubtedly been in the interests of the health of individuals and the general public. Clinical research, however, must be ethically acceptable as well as scientifically sound. Ideally, any clinical study conducted anywhere in the world should respect the same internationally recognized ethical standards.

In the years following the Second World War, scientific misconduct and a disregard for ethics were pervasive features of clinical research, and through the efforts of Henry Beecher, Maurice Pappworth and many others this became widely recognized in the 1960s (1, 2). The World Medical Association's Declaration of Helsinki, issued in 1964, was a significant milestone in the effort to eliminate such violations and establish ethical norms. Many countries have incorporated the Declaration in their national legislation. It has also been the source of more detailed national and international provisions such as the WHO Guidelines on Good Clinical Practice. The Declaration has been revised several times, most recently in October 2000, in response to new challenges, which include the following.

In industrialized countries research costs continue to rise steeply, suitable patients are in short supply, and clinical institutions are overloaded with research projects. Sponsors seeking a quicker and bigger return on investment are attracted to countries in which costs are low and untreated patients plentiful (3). Institutions and countries with little experience in medical research, representing diverse cultures and traditions, have thus become partners in multinational studies. It can be difficult to apply ethical principles, however universal they may seem, in developing countries without a tradition of scientific

research or the infrastructure for it. At the same time it is in these countries that HIV/AIDS, malaria, tuberculosis, diarrhoea, respiratory infections and other major diseases are most prevalent, and therefore where medical research on methods of prevention and control is most needed.

Attempts to respond to these pressures have raised hard questions. Is it not exploitative to use for clinical trials populations which cannot afford the products that eventually result from this research, making the benefits available only to the rich? How has the study in question affected the research subjects, their communities, or health care in their own country? Was there any agreement to make the new treatment available in the country concerned? If so, for how long? Is the new treatment affordable and sustainable there?

The revised Declaration of Helsinki (see pp. 373–374) attempts to respond particularly to questions of this kind, although consensus has been difficult to achieve. Article 19 of the Declaration states: "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 Declaration does not call for any plan or prior agreement between the sponsor and the host country to this effect, however.

Article 30 states that at the conclusion of the study every patient participating in it should be assured of access to the best proven therapeutic method identified by the study. Some object that for a sponsor and researcher this could mean a costly long-term commitment, which would deter them from undertaking the research.

Apparently the most contentious issue in the revision of the Declaration was the role of the placebo. According to Article 29: "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". More flexible wording might have been preferable.

Placebos have been, and will continue to be, used in clinical trials of drugs for

diseases or disorders for which the "best current therapeutic method" is available but needs to be challenged in a further study. It is considered ethical to delay or omit the use of an available treatment in order to conduct a placebo-controlled trial, provided that only temporary discomfort and no serious adverse consequences are expected, and that the study participants are fully informed about alternative forms of treatment and their right to opt for them (4). Examples of such studies are clinical trials of analgesics, hypnotics, anti-emetics, antihistamines, or weight-reducing drugs. Placebo may also be crucial for "add-on" studies, in which the treatment to be tested and a placebo are each added to a standard therapy. A further difficulty is that if Article 29 is interpreted liberally, one may ask how two locally available and affordable traditional medicines may be compared, or how a herbal product may be tested against a commonly used pharmaceutical product that is not necessarily the best current therapeutic method.

On these points and others, the revised Declaration of Helsinki has stimulated lively debate. Clearly it is time for effective self-regulation within multinational health research, and for both sponsoring and host countries to cooperate systematically in reviewing and assessing the ethics, public health value and scientific soundness of research proposals. A major priority now is to build up national capacity for scientific and ethical review, and to establish and support competent ethical review committees in all countries that host multinational studies. ■

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4. Guideline E10: choice of control group and related issues in clinical trials. *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical for Human Use (ICH)*. Geneva, International Federation of Pharmaceutical Manufacturers Associations, 2000 (www.ifpma.org/pdfifpma/e10stepp4.pdf).

¹ Secretary General, Council for International Organizations of Medical Sciences (CIOMS), c/o WHO, 1211 Geneva 27, Switzerland.