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Editorial: **The 5th Amendment of the Declaration of Helsinki: implications for medical research in developing countries**

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Many of us involved in research on tropical diseases have been confronted with the dilemma of defining what is ethically acceptable and what is not, as research often involves fundamental conflicts between ethical principles. The Declaration of Helsinki, drawn up in 1964 by the World Medical Association (WMA) and recently amended for the fifth time (October 2000) (http://www.wma.net/e/policy/17-c_e.html), defines ethical guidelines with the goal of protecting human subjects involved in medical research. Historically, the Declaration stems from the Nuremberg code that was formulated in 1947 as a reaction to unethical medical experiments conducted by Nazis on concentration camp inmates. It has no inherent legal authority but is referred to by many regulatory bodies involved in biomedical research and by medical journals too.

The Declaration of Helsinki in its most recent version comprises 32 sections on the ethical principles for medical research involving human subjects. Besides statements which everybody will readily agree on, such as the duty to conduct scientifically sound and reliable research, the need to act in the participant's best interest or the need to respect his or her autonomy, there are more controversial sections. These leave room for different and sometimes conflicting interpretations which can have important consequences, particularly for medical studies conducted in developing or poor countries. In Section II.3 of the previous version it was stated that 'In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method'. A placebo-controlled trial of short-course zidovudine given to HIV-infected pregnant women to prevent perinatal transmission has been strongly criticized on the basis that no patient participating in a trial supported by US funds should be denied the 'standard care' (not a placebo) available in the US (Lurie & Wolfe 1997). It has also been said that such a trial infringes the basic principle that doctors should not harm their patients (Anonymous 1997).

In the latest version of the Declaration this section has been reworded but still states that 'the benefit, risks, burden and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods'. The problem arises when one needs to define what is the best current therapeutic method. Is this what is internationally available or is it the therapy usually available where the trial is being conducted? The former interpretation would exclude proper evaluation of appropriate though – relative to developed countries – suboptimal interventions that have been shown to reduce mortality and morbidity in poor countries (Aaby *et al.* 1997). An important point to consider is that the annual health budget in most developing countries is less than US$ 10 per head. Of the US$ 56 billion spent annually on medical research worldwide, at least 90% is spent on the health needs of the richest countries, which represent a mere 10% of the world's population (Nuffield Council on Bioethics 1999). In this context research should respond to the health needs and the priorities of the local communities (CIOMS WHO 1993); it should look for relevant and affordable interventions that improve the chances of survival in places where the best available option may be 'nothing' (Gambian Government/Medical Research Council Joint Ethical Committee 1998).

Nevertheless this should never become an excuse for withholding a known feasible and affordable intervention from study subjects just because the local government does not currently provide it. A clear example is antimalarial chemoprophylaxis in pregnant women living in endemic areas. It is now widely accepted that case management

alone is not effective in preventing the adverse effects of malaria during pregnancy and that protection should be offered to all pregnant women (Anonymous 1999). Considering that protection consists of either weekly chemoprophylaxis or intermittent treatment, one of these two options should be offered to any pregnant woman living in an endemic country and enrolled in a research protocol, regardless of government guidelines.

Specially appointed ethical committees have a crucial role in deciding whether a proposed protocol is relevant and ethically acceptable. The latest version of the Declaration of Helsinki expands their role by giving the committees the right to monitor ongoing trials while the researcher is under obligation to provide monitoring information, and especially any serious adverse event. While this is a welcome addition, it raises a number of important issues, particularly on how this could be put in practice. Mechanisms and procedures for local ethical review in some developing countries are under-developed and the very countries likely to be most vulnerable to unethical or exploitative clinical research may be those with the least developed review system (Nuffield Council on Bioethics 1999). Resources for ethical review are obviously needed, particularly if committees have to be more active in monitoring ongoing trials. It is unclear who should provide these resources and the question on how to guarantee independence while receiving an appropriate financial compensation remains. Furthermore, representatives of local communities where the research is to be carried out should be full members of the ethical committees. Unfortunately, this is not necessarily true in many developing countries for a variety of reasons.

In section 19 the Declaration of Helsinki states that 'medical research is only justified if there is a reasonable likelihood that the population in which the research is carried out stands to benefit from the results of the research'. Section 30 specifies that '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'. These two new sections further emphasize the fact that only research questions arising from local health problems are ethically acceptable and that researchers' responsibility towards study participants does not end with the study. Although these additions go further in protecting vulnerable populations from clinical trials on drugs essentially targeted to other users, they also raise questions with no obvious answer. Should a therapy or procedure found to be effective be provided to the study subjects and to the local population after the trial is over? Who is responsible for such a decision and for how long it should be provided? Logistical and financial constraints to adopting new treatments or interventions on a population-wide basis might, at times, be almost insurmountable. Hence the idea that a trial should not be undertaken unless there is a guarantee that the product will be made immediately and widely available carries the risk of limiting the development of new and effective methods.

A very important part (Sections 22–26) of the Declaration of Helsinki deals with the informed consent of individuals participating in research. Consent should be genuine and therefore freely given. However, where the basic health system is poor or nonexistant, the possibility for study subjects to gain access to certain services is a strong incentive to participate. Can their consent be considered truly voluntary? Furthermore, some concepts such as the administration of a placebo or the randomization process might be extremely difficult to explain to people belonging to a different culture, and it may take weeks or months for participants to truly understand the concepts of a clinical trial. One possible solution is a short consideration period prior to implementation of the study to allow participants enough time to understand and decide (Ramjee *et al*. 2000). A particular problem arises from studies where interventions are implemented at community and not at individual level. Should informed consent be sought from communities representatives or from single individuals belonging to those communities? The answer to these questions will probably vary according to the local conditions and the local ethical committee has the important role of deciding what is acceptable and what is not in their specific context. Hence the importance of including community representatives in the ethical committee.

Questions about the ethics of medical research sponsored by international drug companies and conducted in resource-poor countries have started to attract the attention of the lay press (Boseley 2001). Research partnerships where one partner is dominant in terms of funding and organization may lead to compromised ethical standards and exploitation of both researchers and research participants (Nuffield Council on Bioethics 1999).

Documents such as the Declaration of Helsinki should be seen as general guidelines to safeguard ethical principles. They cannot be interpreted without taking into account the local context and this should be done by stimulating an open and transparent discussion. Local ethical committees must have a pivotal role in deciding what is ethically acceptable in their own context and they should be strengthened. Several initiatives for training and networking have already been launched. But the problem of funding the necessary resources for their functioning without infringing their independence remains, and solutions are urgently needed.

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