

A new look at international research ethics

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*Editorial
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The normal "standard of care" against which new interventions are tested in medical research has not been formally defined. It is usually taken to mean the "best proved treatment" for any condition under investigation in a trial. We reject the arbitrariness of this notion of the standard of care and offer a more comprehensive alternative. Use of this new standard invokes a new approach to international research ethics that focuses on reducing inequalities in global health.

The debate on what constitutes a fair and reasonable standard of care for subjects in developing countries who participate in clinical trials has been rekindled by critics of studies on the transmission of HIV.¹⁻³ They argued that placebo controlled trials of new regimens to prevent the vertical transmission of HIV were unethical because they included a placebo arm rather than "the best proven treatment" available in developed countries. Some commentators considered the criticisms to be unfounded⁴⁻⁶ and associated with imperialistic attitudes.⁷

The debate made it clear that the high standards of research aspired to have not been adequately defined. It was also marred by simplistic notions of ethics. Although there was justified concern that pressure from the US Food and Drug Administration could "dilute" the Declaration of Helsinki, critics also presumed that whether a trial was ethical could simply be deduced from the text of a declaration. But declarations—such as the Declaration of Helsinki, governing international research ethics—are like constitutions, needing interpretation. Determining what is ethical goes beyond merely following prescriptions and requires moral reasoning; consideration of all relevant aspects of the case in its context, weighing and balancing competing moral requirements, and developing justifiable conclusions.

Although more mature insight is gradually emerging into the complexity associated with the ethics of research in developing countries, the debate remains incomplete for several reasons.⁸⁻¹² Firstly, there has been a failure to define adequately the "standard of

Box 1: Expanded concept for standard of care

- Provision of the same access to research, expenditure on the total care of each subject, and therapeutic drugs shown to be most effective in other locations
- Provision of the same "hotel" facilities, access to technology, general medical care, and other external influencing factors during the trial that were associated with and contributed to the "best proven" use of the drugs elsewhere
- Provision of the same follow up facilities for subjects after completion of the study and the same access to ongoing care
- Research undertaken by a team of the same culture and language group as the subjects, so that the same degree of effective communication, trust, and genuine informed consent is achieved through a legitimate informed decision making process
- Care provided by a research team with equivalent qualifications, training, and expertise

Summary points

The standard of care for subjects participating in clinical trials is not well defined

Excessive reliance has been placed on international declarations to define what is ethical, but declarations, like constitutions, need to be interpreted

International researchers must develop a deeper understanding of the context within which their research is being conducted

An expanded concept for standard of care is offered that takes account of the context of the trial and is sensitive to the social, economic, and political milieu

National and international bodies concerned with research ethics need to confront the greatest ethical challenge—the enormous inequities in global health

care." Secondly, it has been incorrectly assumed that the standard set by developed countries can be considered the norm. Thirdly, few commentators on research ethics have taken into consideration the injustice of 90% of all medical research being undertaken on those diseases that cause 10% of the global burden of disease.¹³

How do we define "standard of care" for research subjects?

Equal standards of medical care during research, reflecting equal respect for the dignity of subjects, could be taken to mean any one or a combination of several requirements (box 1). It is arbitrary and not justifiable to select only one of these—for example, which drugs are used—to compare the standard of care in developed and developing countries.

In the context of the disputed studies on HIV transmission, the vehement emphasis on the "best proven drugs" eclipsed considerations of whether the drug regimen could be safely applied in different settings. Little attention was paid to the fact that there were many differences between pregnant women in developing countries and those in countries where the "best proven" treatment had been established. Pregnant women in developing countries present to antenatal clinics much later in pregnancy than the women in the original studies; they are often anaemic and malnourished, and they live within a context in which breast feeding has different implications for newborn infants. Moreover, advice not to breast feed would contradict years of intensive education by the World Health Organization.

Concerning the use of placebos, the approach has also been simplistic. Whether a placebo arm is justified in a trial requires careful consideration of potential harms and benefits in specific contexts and cannot be simply deduced from a general declaration.⁷ Of course it is necessary to acknowledge that many placebo trials are unethical because they are undertaken largely for marketing purposes—to show that “me too” drugs have actions greater than placebo, rather than to study whether they are better than existing similar, and often cheaper, drugs. Not only should nothing be done to make it easier to do such trials, but also every effort should be made to reduce wasting time and money on “promotional studies.” In those situations where there are good reasons for placebo controlled trials, these should be considered on their merits rather than be precluded by a bluntly designed exclusive clause in a declaration.

Considerations of context are required aspects of moral reasoning in the application of universal principles in specific situations and do not entail moral relativism. Failure to distinguish moral relativism from the morally relevant considerations of context that are necessary for the specification of universal principles shows a lack of knowledge of the ethical decision making process.¹⁴

Is the blanket application of a universal standard of care achievable?

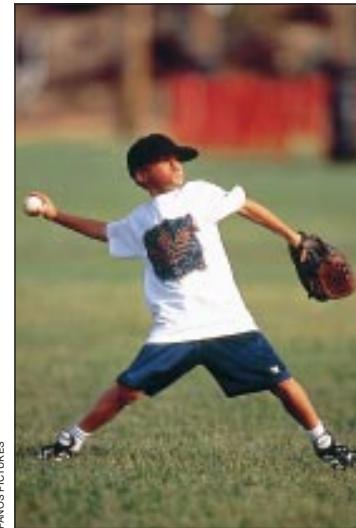
The standard of care may not be achieved in practice, even in developed countries.¹⁵⁻²⁰ In recent months medical research in several US universities has been closed down when several ethical shortcomings associated with a trial were uncovered after the death of a young man with a rare metabolic disorder who agreed to participate in a trial of gene therapy.²¹

It may be even more difficult to achieve the standard of care in practice in developing countries. It would not be possible to meet all the elements shown in box 1 in any developing country. Moreover, the whole “package” may be either irrelevant to the needs of research subjects in their context or not necessarily the best way to spend the resources in the interests of their society.

The United States's standard of care should not be emulated throughout the world. The United States spends 50% of annual global expenditure on health care on 5% of the world's population.²² This level of expenditure is not sustainable as a universal model. Another aspect of the United States's standard of care that should not be emulated is “defensive medicine” to protect against litigation.

An alternative concept of standard of care

A standard of care that could be achieved globally despite economic inequalities and that may assist in reducing such inequalities requires a redefinition of the standard of care (elements of which are shown in box 2) and recognition of some of the special problems associated with clinical trials in developing countries.²³⁻²⁵



Narrowing global inequity is the greatest ethical challenge in health research and health care

Making moral progress in international health research

It will not be possible to achieve the proposed new standard merely by tampering with research declarations or by advancing the simplistic notion that ethical behaviour can be deduced from or promoted by such declarations. A broader moral agenda is required. To achieve this it is important to recognise the potentially exploitative nature of research in developed and developing countries and to have insight into the economic policies that are currently widening the disparities in human wellbeing through their impact on development, the health of populations, and the provision of health care for individual patients.^{13 26 27}

Both to diminish the exploitation of subjects living under inhumane conditions and to respect the dignity of subjects, greater emphasis will need to be placed on certain processes (box 3). The highest achievable standard of care (see box 2) should be the goal. Reasonable limits can be negotiated in specific contexts. The objective should be to ratchet the standard upward rather than to set utopian ideas that cannot be met.

Towards a new research ethics

Traditional research ethics is rooted in responses to abuses of research, such as the Nazi atrocities that

Box 2: Elements for consideration in redefining “standard of care”

- Respect for the dignity of all subjects
- Doing what is in the best interests of the subjects—that is, researching those diseases that commonly afflict them
- Aiming for a distribution of risks and benefits that takes into consideration the potential magnitude of benefit to sponsors (to ensure that “research sweat shops” do not become the norm in a globalising world)
- Obtaining meaningful informed consent in the subjects' home tongue and with an understanding of their world view or value system
- Only undertaking research that will be of benefit to the community being researched
- Translating research findings into components of accessible care in the community being researched
- Avoiding conflicts of interest and exploitation

Box 3: Requirements for making moral progress in international health research

- Educating researchers and members of research ethics committees about research ethics
- Ensuring that international researchers understand and are sensitive to the social, economic, and political milieu that frames the context in which their research is taking place
- Involving members of the host country in the design and conduct of the trial
- Ensuring that trials are of direct relevance to the health needs of the host country and that the balance of benefits and burdens of the project are fairly distributed
- Conducting prior evaluation by a local committee or governing body of whether the study findings can, and will, be incorporated into the local healthcare system
- Providing subjects with care or treatment they would not ordinarily get in the country where the trial is carried out
- Ensuring existing disparities are not more deeply entrenched by inappropriate deflection of local human or material resources away from the healthcare system in the host country towards the research project
- Ensuring that research produces benefits for the practice setting and builds the capacity of healthcare professionals in the host country

resulted in the Nuremberg code and the Tuskegee experiment (where African Americans were deliberately denied effective treatment for syphilis) that led to regulations concerning research ethics in the United States. The protections need to be extended to address systemic deprivation of research subjects through poverty and other threats to freedom.

Those who are involved in international research should be required to have some understanding of, and be sensitive to, the social, economic, and political milieu that frames the context in which their research is taking place and that greatly influences the health of their research subjects.²⁶⁻²⁸ This should include knowledge of (a) the sociology of pharmaceutical research; (b) the political relation between the sponsoring and host countries—for example, how the host country fits into the sponsoring country's foreign policy, what economic aid is provided, the nature of any debt relations, and the extent of arms trading between the two countries; and (c) the human rights' achievements of the sponsoring and host countries. Lessons learnt from a genuinely collaborative research endeavour could be used by international investigators. For example, they might influence political leaders in their countries to promote more equitable relations with the host country in which the research was conducted.

There is thus a need to go beyond the reactive research ethics of the past. A new, proactive research ethics must be concerned with the greatest ethical challenge—the huge inequities in global health.²⁹ Research ethics must be more deeply rooted in the context of global health. It must more forthrightly address the social, political, and economic forces that widen global inequities in health, and it must ultimately be concerned with reducing inequities in global health and achieving justice in health research and health care.

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Corrections and clarifications
Effect of 1995 pill scare on rates of venous thromboembolism among women taking combined oral contraceptives: analysis of General Practice Research Database

A small error persisted to final publication of this paper by R D T Farmer and colleagues (19-26 August, pp 477-9). In table 2 the upper limit of the confidence interval for the age adjusted ratio for the 25-34 age group should be 1.46 (not 1.96).

Birth characteristics of women who develop gestational diabetes: population based study

A glitch in electronic processing led to a problem with reference numbers in this paper by Grace M Egeland and colleagues (2 September, pp 546-7). No reference numbers appear in the text of the printed article, but they can be seen on the *BMJ* website (<http://bmj.com/cgi/content/full/321/7260/546>).

Systematic review of studies of patient satisfaction with telemedicine

An antipodean mix-up occurred in this article by Frances Mair and Pamela Whitten (3 June, pp 1517-20). In the table (p 1528) the study by Oakley et al (reference 9) was ascribed in the far right hand column to Australia, whereas in fact it was conducted in New Zealand.