DISCUSSION

The revised Helsinki Declaration: is it enough?

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Inequities in global health care, an increasing disease burden with decreasing availability of affordable remedies in the developing world, uneven public allocations for health, and the commercial demands of the pharmaceutical industry - all these have fed into an intense debate on the ethics of health research.

These fundamental questions have become narrowly focused. Some of them relate to the funding of trials for diseases rampant in the developing world, the expected standards of care during the trial, the study population's post trial benefits and the availability in the community of affordable treatments. These questions were asked of research responding to the HIV epidemic in the third world. Trials conducted over the last decade in sub-Saharan Africa and South Asia provoked criticism, as they were considered exploitative and unethical (1,2,3).

It was amidst these intense international debates that the Declaration of Helsinki was revised for the fifth time in October 2000. The focus of the debate amongst the medical community has now shifted to the revised Declaration. The new revision attempts to define strict ethical standards of research with strong, carefully selected, words.

Studies in the industrial world satisfied the previous version of the Helsinki Declaration. Many argued that the Asian and African studies would have never been approved in the West; it was unethical to have conducted them with impunity in the developing world. One might ask why such studies were ever conducted in the developing world when guidelines were present prohibiting them. Surely it was not a lacuna in the Declaration itself or in other guidelines. Will revised declarations - and perhaps legislation - prevent unethical research in the future? Will the world become more ethical by revising declarations? Or is the problem something more than a simple lack of guidelines? Opposing groups are at loggerheads fighting battles of attrition. They seem to measure their success according to their ability to add or delete words from declarations. When celebrating these trivial gains, they are oblivious of the greater and grim picture of global health care.

Let us first examine the changes in the Declaration of Helsinki which claim to ensure marginalised research subjects protection and freedom from exploitation.

Clause 19 states that "Medical research is only justified if there is reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research." A number of things are not clear in this clause and need interpretation. What is a reasonable likelihood? How reasonable is reasonable? It states that research populations should 'benefit from the results of the research'. A Phase II or even a Phase III trial conducted anywhere in the world does not project the price of the drug. How is one to assess whether the research population would benefit from this research? The eventual price of the drug may be beyond the reach of the researched population. Researchers argue that initially the prices are high due to the expense on research and development, but that the prices eventually do come down.

Another interpretation of this clause is that the study should be responsive to the health needs of the country where the research is carried out. To be useful and ethical in this situation, a clinical trial in a developing country must use a control that is relevant to the country (4). This means, in most situations, a placebo. Does this mean that the Declaration of Helsinki accepts different standards of care? It is evident that such ambiguities will open doors to all kinds of interpretations to suit everyone's interests. Clause 29 states, "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." This is the most contentious clause of all. It raises major scientific issues regarding the randomised, placebo controlled trial (RCT). RCTs are generally considered the gold standard as they provide the best scientific evidence in a relatively short duration and are considered economical. Active control designs while useful and appropriate in many diseases often cannot provide reliable information on new treatments (4). Such designs are considered to weaken the evidence and thus science. Scientists believe that as medicine advances, evidence to show the difference between therapies is marginal. Such differences can be picked up within in a short time only by randomised, placebo controlled trials. Active control trials, where best options would be employed, require large numbers, continue for long periods, and in some cases could be an exercise in futility (5).

One may ask why it is necessary to have the strongest possible evidence. Should one really lower ethical standards in the interest of science? Why should we not accept equivalency trials instead of randomised placebo controlled trials? (6) The clause not only disallows the use of a placebo where treatment options are available, it also expects that people in the control arm receive the best current treatment. Should this be the best current treatment in the West or the best that is locally available? Providing the locally available standard of care can be considered a violation of the principle of justice. On the other hand, if one permits the use of placebo controlled trials when options are available, impoverished populations in developing countries - who are unable to afford the gold standard treatment - will become a human laboratory. Placebo controlled trials can be conducted there because the locally affordable care is often nothing more than placebo (7). This clause is also criticised by some as an impediment to identifying alternative treatments that are both affordable and effective, even if somewhat less effective than the expensive treatment available in the West. This is an important public health goal for developing countries, and a research priority for many international funding agencies (4). For example, suppression of breast-feeding to prevent transmission of HIV has major implications in developing countries. Generalising this practice would mean losing all that WHO has achieved after years of hard work. Women with HIV will be easily identified and stigmatised. Certainly, the standard of care in the United States - which is dominated by the practice of defensive medicine against litigation (8) - should not be emulated

throughout the world. It is not sustainable. Then what should the research design be? What standard of care should be offered to research participants?

In biomedical research, compromises have tended to reduce ethical requirements and sacrifice human value to ensure the 'best' science (7). Does clause 29 really protect research participants from exploitation? Or is it an impediment to finding remedies affordable and relevant to the needs of the developing world?

Finally, clause 30 states, "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." This needs many clarifications. What does one understand by 'assured access'? Is it free access? For how long? If an anti-hypertensive 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 case 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 (10). This again raises questions which have no obvious answers.

Unfortunately this document does not provide much respite to the developing world. During the discussions, there has been a sense of reluctance to look beyond the obvious. Maybe what is distant is difficult to change but then why bother with half-baked remedies which are unlikely to work at their best?

The statistics on health care inequities are telling. The majority of the developing world spends less US$10 per head on health. Of the US $56 billion spent annually on medical research worldwide, at least 90 per cent is spent on the health needs of the richest countries, which represent a mere 10 per cent of the world's population (11). The result is severely stunted health care in developing countries, further worsened by the burdens of illiteracy and poverty.

Ethical Review Committees (ERCs) in some developing countries are likely to be most vulnerable to unethical or exploitative clinical research. Unfortunately these ERCs may have the least developed review systems (10). More important, researchers in developing nations derive substantial individual and institutional benefits from sponsored research, irrespective of their status as initiators of, or collaborators in, such research (6). Because of this conflict of interest, the importance of ERCs' integrity, independence and capacity for ethical review cannot be overemphasised. The fact that existing mechanisms provide minimal monitoring of research aggravates the potential for exploitation even in well-off countries. These issues call into question the ability of developing countries to conduct independent, competent and quality ethical review and monitor researchers' compliance of approved protocols.

The pharmaceutical industry

The discussions are inadequate without a mention of the role played by the pharmaceutical industry, which operates like any other industry. Its investment decisions are based on the need to maximise returns. As such, it responds to economic demands rather than to statements on social or human needs (9). It is necessary to reflect on the role of the pharmaceutical industry in world health, particularly its business in the 'third world', where up to 50 per cent of people do not have access to even the most basic drugs (10). This is summed up in the regrettable statement that two-thirds of the world's population is "superfluous from the perspective of the market. By and large we do not need what they have; they can't buy what we sell" (11). Research problems are compounded by the fact that the interaction between the medical profession and the pharmaceutical industry has long been a contentious issue. In the US, pharmaceutical companies spend more than $11 billion annually promoting and marketing drugs - between $8,000 and $13,000 per physician. This process has been shown to affect prescribing and professional behaviour (12).

All these questions stem from global inequities in health care, an issue which is consistently ignored. On the other hand, some believe that the economic, social, technological, and political disparities that weigh so heavily on this discussion should not be used as reasons to undermine it (13). Ijsselmuiden (7) "stresses the need to recognise the human rather than economic or scientific primacy, the consideration of alternatives to arrive at what is optimal, just and sustainable, and therefore, relevant to human progress especially in underdeveloped countries." On the other hand Singer and Benatar (8) suggest that "new proactive research ethics must be concerned with the greatest ethical challenge - the huge inequities in global health. Research ethics 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." Certainly research ethics should never be weakened by imperatives like economics, relevance and affordability. But this argument seems too abstract. How can one separate the ethics of health care from that of health research? Who will act to regulate the pharmaceutical industry? Who will look at the ethics of international monetary agencies responsible for the fiscal mess in developing countries? Their policies of structural adjustment have led to an increase in poverty and social inequity. Comparatively few resources have been allocated to health care and health research (14).

The remedies being suggested are trying to treat the symptoms of the disease, which is deeper rooted and needs more than guidelines and declarations. It is like child labour. Nobody in his right mind would ever support it, but an overnight boycott of products from industries which

employ children will surely condemn those children to poverty. Is it more ethical to boycott the products or to do something about the cause of the problem?

We do not think it is unethical in this part of the world to deny liver transplantation to a patient dying with end stage liver disease, which is the standard of care in the West. At the same cost, we could save thousands of children dying of diarrhoea and dysentery. This is a question of setting priorities when there are limited resources. What is principally, ethically and morally wrong has to be judged in the local context, unless we believe we are living in an ideal world. The concept of universality of care is merely a slogan, whether in research ethics or in health care ethics.

If we are actually going to make any difference to this world, which is divided mainly on economic lines, we shall have to make a genuine attempt to reduce these disparities. The economic giants of this world (G7) need to do more about the poor. They must stop the economic strangulation of the world's poor majority to meet their geopolitical goals. They must avoid instigating proxy wars in the developing world to establish their economic and geographical hegemony. The West also must put an end to detrimental fiscal policies and economic exploitation by international monetary agencies which have so far only kept borrowing countries on the verge of bankruptcy. Their policies have only been successful in increasing indebtedness. Has any country in the world been able to break the vicious cycle of 'borrowing for debt servicing'?

oThe developed world has a duty to examine the ethics of the pharmaceutical and biotechnology industry. This 'industry' must be harnessed in order to reduce its hegemony. The giant mergers currently taking place are a bad omen for the poor majority of the world. One wonders if the products of this industry will ever be accessible at an affordable price in the developing world. If there is any honesty of purpose, at least essential and life saving drugs should be available at cheap prices in the developing world. Or they should be exempted from patent laws. The relation between medicine and the industry should be expressed in clear international guidelines serving the interests of global health care.

oThe WHO must play a more proactive role in global policy decisions on resource allocation for health care and health research, geared to the needs of the developing world. Major donor and funding agencies need to prioritise their investments according to the problems faced by the majority of the world.

oThere is a dire need to develop and strengthen the capacity to review research in developing countries if there is an honest desire to protect poor subjects of research in developing countries.

I have no hesitation in admitting that all this is a tall order. If there is an earnest desire to genuinely improve the ethics of health care and health research one will have to explore and debate issues honestly, appreciate and comprehend the gravity and cause of the problem and act by not only empathising but with some action. Anything short of this would simply amount to rhetoric, hypocrisy and ethical imperialism.

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