

# Ethics in international health research: a perspective from the developing world\*

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**Abstract** Health research plays a pivotal role in addressing inequities in health and human development, but to achieve these objectives the research must be based on sound scientific and ethical principles. Although it is accepted that ethics play a central role in health research in developing countries, much of the recent debate has focused on controversies surrounding internationally sponsored research and has taken place largely without adequate participation of the developing countries. The relationship between ethical guidelines and regulations, and indigenously sponsored and public health research has not been adequately explored. For example, while the fundamental principles of ethical health research, such as community participation, informed consent, and shared benefits and burdens, remain sacrosanct other issues, such as standards of care and prior agreements, merit greater public debate within developing countries. In particular, the relationship of existing ethical guidelines to epidemiological and public health research merits further exploration. In order to support health research in developing countries that is both relevant and meaningful, the focus must be on developing health research that promotes equity and on developing local capacity in bioethics. Only through such proactive measures can we address the emerging ethical dilemmas and challenges that globalization and the genomics revolution will bring in their wake.

**Keywords** Research; Research design; Health services research; Ethics; Bioethics; International cooperation; Developing countries; Informed consent; Consumer participation (*source: MeSH, NLM*).

**Mots clés** Recherche; Projet recherche; Recherche en santé publique; Ethique; Bioéthique; Coopération internationale; Pays en développement; Consentement éclairé; Participation consommateurs (*source: MeSH, INSERM*).

**Palabras clave** Investigación; Proyectos de investigación; Investigaciones sobre servicios de salud; Ética; Bioética; Cooperación internacional; Países en desarrollo; Consentimiento consciente; Participación comunitaria (*fuentes: DeCS, BIREME*).

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*Voir page 118 le résumé en français. En la página 119 figura un resumen en español.*

## Introduction

Globally, there are wide disparities in economic development, in burden of disease, and in health outcomes (1) and it is likely that the accelerating trend towards globalization, without the requisite safeguards and protection of human rights, will only worsen these health inequalities. Health is the cornerstone of development and “good health is a cornerstone of economic progress, a multiplier of society’s human resources, and, indeed, the primary objective of development” (2). Although the private sector has played an increasingly important role, public health programmes are the key to achieving health goals in most developing countries and decisions about these and other interventions must be based on scientific evidence.

Research funding in developing countries has also been the subject of much attention recently. The Global Forum for Health Research has pointed out that less than 10% of the world’s research resources are earmarked for 90% of the health problems (3). Important steps in redressing this imbalance are to promote equity in health research globally and to strengthen the capacity within developing countries to undertake research that is relevant to them (4). The planning and execution of such research must be guided by the fundamental principles of human dignity and ethics.

Recently, there has been considerable debate about the ethical conduct and reviewing of health research, but this debate has largely taken place among ethicists and researchers in industrialized countries. The views of public health practitioners and researchers from developing countries have been underrepresented. It is the purpose of this paper to review some of the recent controversies in international health research ethics from the perspective of a public health researcher based in the developing world, and to suggest a framework for future action.

## Ethical conduct and regulation of international biomedical research

Much of the recent debate and controversy in international bioethics has stemmed from the recent regulatory processes and international guidelines for the conduct of research. As a concept, the pre-eminence of the rights and safety of patients has been recognized since the time of Hippocrates (5), but they were first enunciated in the context of experimental therapy by Claude Bernard (6). Events during the Second World War, with widespread atrocities committed by Nazi scientists and physicians under the guise of medical experimentation, led to

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global outrage and dictated the need to put forward a code of conduct for human research, namely the Nuremberg Code (7). In 1964, the World Medical Association Declaration of Helsinki took this process a step further and underscored 12 basic principles for the conduct of human biomedical research (8). However, these principles were largely physician-oriented and did not directly address the issue of research in developing countries.

The issue of research in developing countries was eventually taken up by the Council for International Organization of Medical Sciences (CIOMS), which, in collaboration with WHO, proposed guidelines for international research. The guidelines were further amended in 1993 as the *International ethical guidelines for biomedical research involving human subjects* (9) and are presently undergoing further revisions.

Although these guidelines were widely publicized and recognized by agencies involved in human research, their implementation and acceptance remained largely voluntary. This was demonstrated by the discovery that medical researchers deliberately withheld treatment from African-American patients with syphilis in Tuskegee, AL, in the United States of America (10). Following the publication of this information, a national commission was established in the USA to develop principles and guidelines for human research. The consequent Belmont Report (11) drew upon the existing Helsinki Declaration and highlighted three principles: respect for individual autonomy; beneficence; and justice. Over the last few years these guidelines and amendments to the Helsinki Declaration have also been complemented by efforts in industrialized countries, such as the consultations of the Nuffield Council for Bioethics in the United Kingdom (12) and the National Bioethics Advisory Commission in the USA (13).

## Recent controversies in international research and their implications for regulation and guidelines

In 1994, the results of a study on the efficacy of zidovudine were published by the AIDS Clinical Trials Group (ACTG). Study 076 was the first randomized controlled trial of oral and intravenous zidovudine in France and the USA, and the results indicated that zidovudine significantly reduced vertical transmission rates of the human immunodeficiency virus (HIV) from mothers to infants from 25.5% to 8.3% (14). The ACTG study 076 regime soon became the standard therapy for preventing mother-to-child transmission of HIV. However, a panel of experts, subsequently convened by WHO to consider strategies for reducing mother-to-child transmission of HIV, considered the intensive ACTG study 076 regimen too expensive for developing countries and recommended that a simpler regimen be evaluated, using a placebo arm in control populations (15). Soon after, 18 trials of antiretroviral drugs were initiated in different parts of the world, 15 of which used a placebo arm. In September 1997, the use of placebos in these trials became public (16, 17) and this was followed by a prolonged and acrimonious debate on the ethical aspects of such trials. Many ethicists insisted that the trials violated fundamental human rights, whereas other researchers indicated the need for realism and a pragmatic approach to public health interventions for preventing mother-to-child transmission of HIV in developing countries. The publication of the

report of the workshop on perinatal HIV intervention research in developing countries (18) was also followed by letters highlighting the inviolability of the Helsinki Declaration and CIOMS guidelines (19, 20).

The debate has remained alive because of the intransigence of those concerned. Some people refuse to budge from the fundamentals and see the entire issue of international health research through the looking glass of guidelines and regulations. They insist that a single moral standard should govern all research on human subjects, regardless of where and when the research is carried out. Others have attempted to bridge the divide but, notably, the voices of many scientists in the developing world seeking to expand the debate have been largely ignored. The statement of the Gambian Government/Medical Research Council Joint Ethical Committee (21) was one of the few public statements that attempted to enlarge the debate to the broader issues of public health. Although these debates have led the USA and agencies to review the regulation and oversight of internationally sponsored research (12, 13), it is debatable whether these reviews have been aware of the wide range of opinions from the developing world. It can also be argued that while the concerns about research in developing countries have brought a welcome focus on this long-neglected area, the focus has been on regulatory issues, rather than on the basic problems that underlie the inequities in health and human rights in developing countries.

## National or international guidelines for ethical conduct of research?

Some of the debate surrounding the ethical regulation of international research indicates that while issues of study design, ethical review, and standards of care have been highlighted, the underlying socioeconomic deprivation and inequities are largely ignored. Additionally, much of the debate has centred on externally sponsored and international research, while a large percentage of research in developing countries is indigenously sponsored and regulated by local rules and guidelines. The recent guidelines of the Indian Council for Medical Research for the ethical conduct of biomedical research are a case in point (22). The guidelines were the product of consultation and public debate over several years and are an example of how such a process can facilitate the ethical conduct of research.

In other parts of the developing world, the capacity to develop local guidelines may either not exist or be deemed unnecessary given the plethora of international guidelines. Although the Helsinki Declaration and CIOMS guidelines are not legally binding on nation states, they do have moral validity and ostensibly influence research policy by most international funding agencies and the pharmaceutical industry. It is thus inevitable that these existing international guidelines will continue to form a cornerstone of research ethics in much of the developing world. The key issue is the application of the true spirit of these guidelines and a contextual interpretation of their recent amendments. Many of the broader concepts of public health policy and decision-making are based on a larger, objective, utilitarian assessment of greater public good, rather than on individual subjective assessments. It is in this field of public health that the application of the broad principles of ethics of public health lags far behind those of the ethics of the individual, and is not sufficiently addressed by existing

guidelines (23). Most recent debates on international research ethics have centred on the specifics and semantics of terminology and have largely focused on individual rights, rather than on broader issues of public health.

## Specific issues in the ethical conduct of research in developing countries

### Community participation

Research needs to respond to community needs and national priorities, and the development of a national research agenda in developing countries must be firmly grounded in a process of priority setting (24). However, a larger and more difficult challenge is to involve the communities themselves in the research questions and to link the research to their own development. Such a participatory process with the community is a continuum that includes community consultation in protocol development, appropriate information disclosure and informed consent, protection of confidentiality and right of dissent, and community involvement in the conduct of research (25).

This participatory framework largely pertains to public health and applied research, but as the world shrinks, many research projects may focus on broader regional priorities, rather than on narrower issues of local interest. It is thus imperative that reasonable means and terms of engagement be found that respond to the needs and concerns of populations (26), in a process of participatory democracy and freedom of expression. Such a participatory process of decision-making may also enhance the prospects of achieving a fair balance in the distribution of a nation's biomedical research resources. If a country's health research system could be regarded as the "brain" of its health system, then ethics would constitute its "conscience". It is imperative that such health research systems function to the highest aspirations of ethics and distributive justice.

### Prior agreements and benefits of research

Prior agreements and assurances about the benefits of research products have received less attention than the practical aspects of protocol development and study design. The commentary on CIOMS guidelines 8 and 15 (9) explicitly state that "As a general rule, the sponsoring agency should agree in advance of the research that any product developed through such research will be made **reasonably available** [my emphasis] to the inhabitants of the host community or country at the completion of the successful testing. Exceptions to this general requirement should be justified and agreed to by all concerned parties before the research begins."

The most recent revisions of the Helsinki Declaration (8), however, take a less stringent position, but declare 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." Others have criticized the CIOMS guidelines as being soft and have argued that agreements need to be explicit and that funding needs to be identified prior to undertaking the research (27). In its most simplistic interpretation, these requirements preclude any large-scale public health research in developing countries, unless these assurances could be provided. The proponents of this approach argue that it would avoid unnecessary and curiosity-driven research, as well as undue exploitation of vulnerable populations in underdeveloped communities.

Those exposing themselves to the risks of research must, at the very least, be assured of access to the fruits of the research.

These assured availability agreements only apply to a narrow band of drugs, vaccines, and other products. They cannot be readily applied to phase I and II drug trials, nor to vaccine trials, and epidemiological and social science research. Another important consideration is the usual time lag before the robustness of research findings can be assured, frequently by replication elsewhere. The benefits of participation in research may also extend beyond the narrow definition of end products, as there may be other significant improvements in the health care system as part of the project. It is also possible that the assurances of such benefits may offer inordinate inducements to poor and impoverished populations and thus represent another form of exploitation. Moreover, a broader definition of benefits as something other than the product of research may be required, since the availability of a product within a dysfunctional health system is no assurance that the product will reach those who need it most. In some developing countries, political doctrine may demand that either all or none of its citizens should have access to a particular product, which makes it almost impossible to make an economic argument for the pharmaceutical industry to pursue research of relevance to developing countries. However, placing such issues at the forefront of research planning, especially if the research has international sponsorship, can expedite making the benefits of research available to the very populations that helped in the development of the benefits.

Given the limited resources for research in most developing countries, stringent application of these criteria and guidelines might make it almost impossible to provide such long-term assurances of benefits or availability of products. This would effectively stop much-needed public health and epidemiological research that often generates precisely the information that might influence future public health policy. The ground-breaking way in which research on hepatitis B (28) and *Haemophilus influenzae* type B vaccines (29) was undertaken in the Gambia, points the way. A participatory process involving donors, researchers, and the Gambian Ministry of health ensured that the vaccination programme could be sustained well beyond the trials. In contrast, evaluation of hepatitis A vaccination in Thailand (30) was not accompanied by any such agreements or plans to introduce the vaccine, nor are such agreements part of current evaluations of the newer typhoid (31) and pneumococcal conjugate vaccines in other parts of south-east Asia and Africa (32).

It is therefore evident that the concept of "reasonable availability" does not settle the issue of responsibility to the community. In its narrowest definition, the concept indicates a simple assurance of the availability of a research product within the local market and includes responsibilities for the care and well-being of the community for a long time. The requirement for extended community care may place an inordinate burden on both governments and other sponsors, effectively stopping all large-scale trials in developing countries, whereas the former situation may open opportunities for exploitation. Actual practice probably lies somewhere in between, with a broader interpretation of the responsibilities and benefits of participating in research.

### Standard of care and the use of placebos

A major issue in the recent controversy surrounding the HIV/AIDS drug and vaccine trials in developing countries is the use

of the placebo arm instead of the ACTG study 076 triple therapy, which was the newly established standard care in industrialized countries at the time. The recent revisions of the Helsinki Declaration (8) clearly state in Section 29 that “the benefits, risk, 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.”

Although some have argued in favour of retaining placebos as the most efficient means of obtaining the requisite scientific information (33), their overall use in health research and therapy is probably overstated. Perhaps the most pervasive argument supporting the continued use of placebos is based on efficiency and economics. The scientific rigour of a placebo-controlled design can be balanced against alternative models of scientific enquiry which, though longer and more expensive, are ethically sound. If journals were willing to accept reports of studies with quasi-experimental designs, and funding agencies were willing to support studies for longer durations, several alternatives to placebo controls can be envisioned.

Although not clearly specified in the Helsinki Declaration, the standard of care can be interpreted in the context of the study location. It can be interpreted as the global standard of care rather than a locally existing standard (34), or a general standard of care in the research setting (13), including aspects of sustainability (35). Others have expanded the definition of standard of care to include additional aspects such as provision of care by a research team with equivalent qualifications, training, and expertise as those in industrialized countries; and research carried out by a team with the same culture and language as the study subjects, to assure effective communication and informed consent (36).

The issues surrounding standard of care have been the subject of much rancour and debate, and highlights the wide disparities that exist in health and economics globally. Some scientists in developing countries have argued that given the abysmal state of health and facilities in many developing countries, the local therapy for HIV infection may well be no treatment (27). Others have questioned the very notion of a global standard of care, given that standard therapy in one health system, with profligate expenditure on defensive medicine, may be totally inappropriate in another system with limited resources (35, 36). On the other hand, the development of protocols for managing acute respiratory infections among children in developing countries has been a tremendous benefit. It can be argued that none of these developments could have taken place had studies employed the western standard of care for treating pneumonia with injectable third-generation cephalosporins. By the same token, although artificial feeding of infants born to HIV-positive mothers is the standard in the West, encouraging this practice in Africa would kill infants due to diarrhoea much faster than HIV would.

### **The Gadchiroli trial**

The recent landmark trial in Gadchiroli, India, makes an interesting case in point (37). Bang et al. undertook an evaluation of domiciliary neonatal care with community-based health workers administering oral trimethoprim-sulfamethoxazole and twice-daily gentamicin to newborn infants with suspected sepsis. A control population was used for comparison and the researchers were able to demonstrate a

72% reduction in neonatal mortality using this approach. This study would have raised ethical questions by most existing standards, since it involved a control population and also used an experimental protocol, when the national standard of care for suspected neonatal sepsis was intravenous antibiotics and supportive care. Bang et al. went through an elaborate scientific and ethical review process prior to the study, involving national experts and the Indian Council for Medical Research. The researchers were also able to get community concurrence to participate in this study, in a situation where even the national “standard of care” was not available to the participants. The benefits of the study for the local people (in terms of improved neonatal survival) and its impact on national and global programmes for neonatal care have been enormous. Taking an extreme position on the standards of care would have required that the study only be conducted with a control arm that received neonatal intensive care and expensive intravenous antibiotics, neither of which are sustainable even in urban settings in India. Thus, the study could not have taken place.

The Gadchiroli trial vindicates the position of public health researchers: each developing country deserves the chance to develop health care interventions that suit local sociocultural and economic means. Such landmark projects form the foundation of a gradual and progressive improvement in the health status of the population, with a participatory assessment of applicable ethical standards. On the other hand, clearly unscrupulous and opportune research, which exploits the vulnerability and needs of a given population, must be condemned. The Trovan<sup>®</sup> drug trial in the midst of a meningitis outbreak in Nigeria (38) and a recent trial in India (39) are examples where the need for ethical guidelines and minimal universal ethical standards for research becomes absolute.

## **The way ahead**

Although recent debates on the ethical dilemmas of health research in developing countries have focused on regulatory issues and have lamented the polarization of views, many see a silver lining. At the very least, the debate has focused attention on the needs of developing countries and the vast inequities in health and human rights. A pragmatic approach towards bridging the gaps necessitates the introduction of several measures, some of which are discussed below.

### **Linking health and research issues with equity**

If the goal of research in developing countries is to improve the health status of the population, thereby reducing the equity gap with more industrialized countries, then applying bioethical principles will aid the process. The inequities in global health and resource allocation are incompatible with the goals of justice, and neither regulations nor guidelines alone can overcome the differences. The partnerships for expanding the role of ethics in global public health and research should involve all current stakeholders, including the pharmaceutical industry. The ethics debates surrounding HIV/AIDS research in developing countries should not be seen in isolation from the controversy surrounding allegations of exorbitant profit on HIV/AIDS drugs by pharmaceutical companies (40).

### **Developing local capacity**

Local capacity could be developed by strengthening models for reviewing the ethics of research, since the capacity for

undertaking research must include the capacity to undertake ethical review of the planned research and its conduct. Local capacity could also be strengthened by developing partnerships, although international and regional networks or partnerships in bioethics are no substitute for local action. In the words of Abdallah Daar “So long as all the ethicists are in the North, and the South is just the recipient of ethical principles, nothing will change!” (41).

A review of the existing capacity in bioethics and in ethical review of research in developing countries reveals major gaps (42). Bioethics training must be strengthened in undergraduate medical education, and in postgraduate and public health training programmes. This will require a major investment in manpower and a new approach to the teaching of bioethics, such as in the United States National Institutes of Health–Fogarty training programmes in bioethics. The immediate need, however, is to strengthen local capacity and manpower by developing innovative training models for ethics that are cost-effective and sustainable. The opportunities afforded by the Internet for learning and education in ethics should also be utilized.

### Working towards true global consensus and ownership

All nation states need to be included in the broader debate about the ethical principles of research within existing health systems. To date, this debate has remained largely within the close-knit circle of ethicists or researchers, and it is time to take the debate to a larger platform, to facilitate the adoption and ownership of ethical principles by developing countries. Although the creation of the Global Forum for Bioethics in Research is a welcome move in this direction, it needs to expand further and include all key constituents and representatives from developing countries. WHO is the logical platform to address issues that require global consensus and agreements, and the WHO-sponsored consultative process on the ethical issues surrounding HIV vaccination trials is an illustration of what can be achieved (43). However, it is not advocated that WHO be forced to play a role in the governance of global ethics, a role that it may have neither the capacity nor resources to fulfil. Instead, ethics should be a core responsibility of WHO when developing international health and research policies with its Member States.

### Determining future ethics

One can safely predict that ethics will assume centre stage in the next few years in both industrialized and developing

countries, especially as the issues of human genomics research and biotechnology move to the forefront (44, 45). While these issues are currently at the core of the ethics debate in industrialized countries, most developing countries are largely excluded from the debate. On the other hand, it is heartening to see the first moves towards understanding the religious and cultural context of ethics in many developing countries (46).

### Conclusion

Bleak and confusing as the field may be, the last few years have been a watershed in international bioethics and the heightened debate has pushed ethical issues surrounding health research in developing countries into the limelight. The challenge now is to develop a sound plan for expanding the ethics debates to the larger issues of global equity and justice, and to make the process as participatory and democratic as possible. It is critical to link issues of health, health research, ethics, and equity as vital components of the same equation. The actions required to move ahead in this field include strengthening bioethics capacity in developing countries; linking health research to community needs in a transparent and participatory process; and increasing communication between scientists and ethicists in industrialized and developing countries. The clear goal in all these activities must be the reduction of global inequities in health. This may take time, but it is the only way to bring about true change in the ethics of international health research, instead of having a superficial debate on the language of regulations. ■

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## Résumé

### Ethique et recherche en santé internationale : le point de vue du monde en développement

La recherche en santé joue un rôle central dans la réponse aux inégalités dans le domaine de la santé et du développement humain, mais pour atteindre ses objectifs elle doit reposer sur des principes scientifiques et éthiques solides. Même s'il est reconnu que l'éthique joue un rôle central dans la recherche en santé dans les pays en développement, la plupart des débats portent maintenant sur les controverses qui entourent les recherches financées par un sponsoring international et ont lieu le plus souvent sans une participation appropriée des pays en développement. La relation entre les principes et réglementations en matière d'éthique et la recherche en santé publique parrainée par des sponsors locaux n'a pas été suffisamment explorée. Par exemple, tandis que les principes fondamentaux de la recherche

en santé, tels que participation communautaire, consentement informé et partage des bénéfices et des charges restent incontournables, d'autres questions, comme les normes en matière de soins et les accords préalables, doivent être davantage approfondies, notamment la relation entre les directives éthiques existantes et la recherche en épidémiologie et santé publique. Pour que cela soit possible dans les pays en développement, il faudra mettre l'accent sur le développement des recherches en santé qui favorisent l'équité et des capacités locales en bioéthique. Ce n'est qu'en prenant de telles mesures par anticipation qu'il sera possible de faire face aux nouveaux dilemmes et défis éthiques qui accompagnent la mondialisation et la révolution génomique.

## Resumen

### Ética de las investigaciones sanitarias internacionales: perspectiva desde el mundo en desarrollo

Las investigaciones sanitarias son de crucial importancia para hacer frente a las desigualdades en materia de salud y desarrollo humano, pero para alcanzar tales objetivos esas investigaciones deben estar basadas en principios científicos y éticos racionales. Aunque se reconoce que las consideraciones éticas ocupan un lugar central en las investigaciones sanitarias en los países en desarrollo, gran parte de los recientes debates se han centrado en la polémica suscitada por investigaciones internacionales emprendidas en gran medida sin contar con la necesaria participación de esos países. No se ha examinado adecuadamente la relación existente entre las directrices y regulaciones en materia de ética por una parte y las investigaciones de salud pública patrocinadas autóctonamente por otra. Así, por ejemplo, mientras los principios fundamentales de las investigaciones sanitarias éticas, como la participación de la comunidad, el

consentimiento informado y el reparto de los beneficios y de las cargas, se mantienen como valores sacrosantos, otros aspectos, como la calidad de la atención o el acuerdo previo, exigen un mayor debate público en los países en desarrollo. En particular, hay que estudiar más a fondo la relación existente entre las actuales directrices éticas y las necesidades de investigación en materia de epidemiología y salud pública. A fin de apoyar en los países en desarrollo la realización de investigaciones sanitarias que sean a la vez pertinentes y valiosas, el objetivo principal debe consistir en concebir investigaciones que promuevan la equidad y en desarrollar la capacidad local en materia de bioética. Sólo con medidas previsoras de esa naturaleza podremos resolver los dilemas éticos que se están planteando y los retos que traerán consigo la globalización y la revolución genómica.

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