Conducting research ethically in developing countries

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Medical research in developing countries funded by those in wealthy countries is crucial but must be subject to rigorous ethical safeguards, according to a report by the Nuffield Council on Bioethics. This article looks at the background to the report, summarizes the current economic context and provides an overview of established regulatory frameworks. It then presents the findings of the report – *The Ethics of Research Related to Healthcare in Developing Countries* – and points out important social and cultural issues that should be taken into account when considering research in developing countries.

Economic context of research expenditure: the 10/90 disequilibrium

The major inequalities in health that exist across the world are closely related to levels of social and economic development. Developing countries urgently need research to help relieve the enormous burden of disease they carry, which includes diseases such as tuberculosis and malaria. However, many countries have limited funds and too few trained staff to conduct their own research (see Table 1).

The disparity in health research expenditures between developed and developing countries was highlighted in the 1990 report of the Commission on Health Research for Development [1]. This group assessed total funds spent on research in different countries and examined the burden of ill health. Their analyses revealed a striking difference between health needs and research expenditures. Using those countries with the lowest mortality rates as a benchmark, they proposed that deviations from these rates in other countries represented potentially avoidable mortality. The amount of avoidable mortality (in terms of years of life lost owing to premature mortality) in developed and developing countries was calculated and compared with the estimated research expenditures of the respective health problems of each country. These calculations led to estimates that 93% of the global burden of premature mortality is attributable to disease problems in developing countries, but that about 95% of global expenditure on health research is directed at the disease problems of developed countries.

Refinements of these estimates by the World Health Organization (WHO) Ad Hoc Committee on Health Research [2] supported the conclusion that the central problem in health research is the '10/90 disequilibrium'. That is, of the $US 50–60 billion worldwide annual expenditure on health research by both the private and public sectors, only 10% is devoted to the health problems of 90% of the world's population [3].

The scope of externally sponsored research

Active participation from many agencies will be required to achieve change. Currently, there is no central audit of externally sponsored research conducted in developing countries. However, organizations such as the US Food and Drug Administration (FDA) and the Pharmaceutical Research and Manufacturers of America (PhRMA) monitor the amount of R&D conducted abroad. Sponsors of research range from governments, government agencies and voluntary organizations (in developed countries), to international bodies such as WHO and multinational pharmaceutical companies. The FDA has recorded a 16-fold increase in the number of foreign clinical investigators conducting research on new medicines in the decade 1990–2000. Numbers grew from 271 in 1990 to 4458 in 1999 [4]. The number of countries in which clinical investigators conducted research increased nearly threefold from 28 to 79 for the same period, with the largest growth occurring in Latin America and Eastern European countries. It is against such a background that research on health in developing countries must be considered.

Social and cultural issues

Developing countries are not a homogeneous group. They differ in their culture, history, size of population and rate of growth, gross national product per capita, technological and other infrastructure, recognition of human rights, and extent of social harmony or disharmony, to name but a few. Many of these factors have significant relevance when considering research in developing countries. More precisely, countries might differ in how they combine modern healthcare with traditional medicine; they might have varying views on the concepts of illness, disease, misfortune, and death, as well as on the doctor–patient relationship and who makes the decisions about taking part in research. It is therefore inappropriate to regard developing countries as a single entity; their diversity must be taken into account when planning healthcare research.

Table 1. A comparison of annual health expenditure around the world

	Annual health expenditure per capita (internat. $[a,b])	Health expenditure as % GNP	Life expectancy at birth Males/Females	Doctors /10^5 popn	Nurses /10^5 popn
United States	3724	13.7	73.8 /79.7	279.0	972.0
Japan	1759	7.1	77.6 /84.3	193.2	744.9
United Kingdom	1193	5.8	74.7 /79.7	164.0	497.0
Chile	581	6.1	73.4 /79.9	110.3	47.2
Brazil	428	6.5	63.7 /71.7	127.2	41.3
Cuba	109	6.3	73.5 /77.4	530.4	677.6
Afghanistan	89	3.2	45.3 /47.2	11.0	18.0
India	84	5.2	59.6 /61.2	48.0	45.0
Sri Lanka	77	3.0	65.8 /73.4	36.5	102.7
Uganda	44	4.1	41.9 /42.4	n/a	18.7
Sierra Leone	31	4.9	33.2 /35.4	7.3	33.0
Somalia	11	1.5	44.0 /44.7	4.0	20.0

[a]Reproduced with permission from WHO (2000) The World Health Report 2000. Health Systems: Improving performance. WHO. Geneva and WHO Estimates of Health Personnel: Physicians, Midwives, Dentists and Pharmacists (around 1998) at http://makeashorterlink.com/?D2271283
[b]International dollars' take into account the local purchasing power of the currency and in developing countries are thus generally higher than the expenditure in US$.

Current guidance and regulatory practice

The conduct of research in healthcare is subject to a wide range of national and international guidelines. *The Declaration of Helsinki*, published for the first time in 1964 by the World Medical Associations (WMA), expresses most prominently the recognition that the integrity of the persons participating in research is paramount [5]. The Declaration, which has been revised five times to date, sets out the principles to be observed in research on human participants in general, and has become the cornerstone of research related to healthcare.

Apart from guidelines that claim general applicability, a wide array of guidance has been established to address more specific areas. The Council for International Organizations of Medical Sciences' (CIOMS) [6] *International Ethical Guidelines for Biomedical Research Involving Human Subjects* was set up in the recognition that special circumstances prevail when research is undertaken in developing countries. The *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use* (ICH) [7] specifically addresses the pharmaceutical industry, and *Ethical Considerations in HIV Preventive Vaccine Research*, published by UNAIDS (Joint United Nations Programme on HIV–AIDS) [8], focuses on research into vaccines for a single disease (HIV and AIDS).

There is, therefore, no lack of guidance on research involving humans, but over recent years there has been increasing criticism because of two reasons. First, some guidelines have proved to be insufficiently nuanced or too ambiguous. For instance, in the context of the controversies regarding standard of care in the perinatal HIV transmission studies in 1997, the same CIOMS guidelines were used by both parties in the conflict to support their opposing views (see [9–11]). Second, most of the existing guidance on research related to healthcare does not have the force of law (although there are exceptions [12–14]). Most guidance, such as the Council of Europe's *Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine* [15], derive their authority through treaty obligations imposed on signatory nations, or are only binding for specific stakeholders, which poses further problems (e.g. the *Declaration of Helsinki* only applies to physicians, and CIOMS only binds its signatory members).

Externally sponsored research raises specific issues, for example, the danger that the conduct of research might fail to reflect the cultural and social values of those from the developing countries who participate. For these reasons, the Nuffield Council on Bioethics sought to consider the ethical issues of research related to healthcare in developing countries. The aim was to provide a framework for those designing or conducting research in developing countries, and to ensure that there is no exploitation of those who take part. The Council set up an international Working Party in 2000, which included experts from medicine, healthcare, anthropology, philosophy, and public policy, from both developing and developed countries.

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The ethics of research

The Working Party sought to establish an ethical framework in the form of a set of principles that would allow them to evaluate the actions and policies of individuals and bodies such as companies, non-governmental organizations (NGOs), international organizations or government agencies. Rather than being part of a more general ethical theory, these principles outline the basic considerations that should be taken into account when planning or conducting research related to healthcare in developing countries, for establishing own guidance and for evaluating existing regulation:

- the duty to alleviate suffering;
- the duty to show respect for persons;
- the duty to be sensitive to cultural differences;
- the duty not to exploit the vulnerable.

The Working Party then went on to apply these principles to the four areas of primary concern that need to be addressed when such research is designed: (1) standards of care, (2) consent, (3) what happens once research is over, and (4) ethical review of research. Each of these areas is discussed in more detail in the following section.

Recommendations of the report

Standards of care

One of the more controversial topics in healthcare research is the standard of care that should be provided to members of a control group. This is particularly vital when, for example, a new treatment or vaccine is being evaluated. The Working Party recommended that, wherever appropriate, participants in the control group should be offered a universal standard of care. This term refers to the best treatment available anywhere in the world, wherever the research is conducted, in contrast to a non-universal standard of care, which refers to treatment available in a defined region.

However, there might be cases where provision of a universal standard is not appropriate. For example, it might not always be deliverable – if the universal standard of care was a liver transplant, the infrastructure in developing countries might be too limited to allow researchers to offer this treatment. Alternatively, the use of a universal standard of care might not give results that are relevant to the population in which the research is conducted. For example, it might be inappropriate to evaluate a new treatment against one that is too expensive to purchase and too complicated to deliver in a country, even if that is the universal standard. In these instances, the challenge is to fulfil the duty to undertake research in a way that is consistent with the principle of not exploiting those who are vulnerable. The Working Party recommended that the minimum treatment that should be offered is the best intervention currently available as part of the national public health system [16]. Exceptions to this recommendation might be justified in very rare cases, for example, where research attempts to establish the ineffectiveness of what currently is deemed to be the best treatment available through the host's country health system by comparison to a placebo [17].

Consent

Misunderstandings can occur when sponsors are unfamiliar with the cultural traditions of the country in which the research is conducted. Researchers are often faced with difficult choices when considering who should make decisions about taking part in the research. For example, in some areas of Uganda, the head of the immediate family is a man (husband or father) and he will usually take the final decision on all matters, especially sensitive issues affecting family members. Family members who do not submit to such decisions might face serious consequences. Thus, in such circumstances, women and children tend not to participate in a study unless permission has been granted by the head of the household. However, in reaction to this tradition, Uganda has set up guidelines that require investigators to obtain 'the legally effective informed consent of the individual research participant'. In addition, they explicitly state that 'a community leader may not consent to the participation of community members' (see [18]).

Sensitivity to cultural differences is crucial, and the Working Party therefore recommends that, in some cultural contexts, it might be appropriate to obtain agreement from the particular community, or assent from a senior family member before any prospective participant in research is approached. However, as the duty of respect for persons requires that we do not act against a person's wishes, it is also important to insist that genuine consent to participate in research must always be obtained from each participant individually. For consent to be genuine, it must be voluntary and informed, which in many cases is more a question of detecting and eliminating a lack of consent (see [19]). Thus, health professionals must do their best to communicate relevant information accurately and in an understandable and appropriate way. The information provided must include, for example, the nature and purpose of the research, the procedures involved and the potential risks and benefits.

What happens once research is over

Many controversies surround the issue of what happens when research is over. Researchers, sponsors and research ethics committees have to consider whether an intervention shown to be successful should be provided to research participants once the research is completed. The Working Party concluded that it is ethically not acceptable for any study to begin without a decision having been made as to whether or not those in control groups will be offered an intervention shown to be successful on completion of the trial where relevant and

appropriate [20]. The lack of such arrangements would have to be justified to a research ethics committee [21]. Consequently, the Working Party endorses the US National Bioethics Advisory Commission (NBAC) recommendation that researchers should endeavour – before the initiation of a trial – to secure post-trial access to effective interventions for participants in the trial.

The provision of an intervention to the wider community once the research is over is a more contentious issue, and the complexity of the circumstances makes it difficult to formulate general guidance. Occasionally, the price of treatments can drop dramatically after research, or an agreement might be reached with a pharmaceutical company that the treatment will be provided free-of-charge for a certain period. However, it was concluded that it is duty of the researcher to address this issue before any research is initiated [22].

Ethical review of research

Robust ethical review of any proposed research provides an essential safeguard for research participants, and further mechanisms must be developed. It is recommended that externally sponsored research projects should be subject to independent review in both sponsor and host countries. This review should assess the scientific validity and ethical acceptability, as well as the relevance to priorities in healthcare within the country [23].

Implementing the recommendations of the Nuffield Report

As outlined previously, inequalities in resources between external sponsors and those in developing countries is often so great that there is a real risk of exploitation. In addition, the various forms of guidance, whether international or national, often do not account for the special circumstances that accompany research undertaken in developing countries. The Working Party discussed two approaches to protecting both the communities and the individuals. First, the development of an appropriate regulatory framework, and second, the need for improved training and education.

As regards a regulatory framework, the Working Party recommended that developing countries should create their own national guidance for clear and unambiguous application, taking into consideration existing guidance. Any new or revised guidance should provide training in the ethical conduct of research for all professionals involved. This should apply to staff in both developed and developing countries, and should take into account the multidisciplinary nature of research [24].

The Working Party also recommended that international organizations, including WHO, continue to expand their current programmes for establishing, training and monitoring the development of research ethics committees. In addition, pharmaceutical companies – together with other external sponsors – should assist in strengthening their expertise in designing and conducting relevant research because interpreting and applying research guidance is an important accompaniment to the guidance itself. Education and training in the ethics of research of all professionals involved in healthcare research, particularly those on research ethics committees, is essential to ensure the requirements of relevant guidance on ethics are met [25]. However, when sponsors provide support it is vital that the independence of research ethics committees be maintained. The Working Party therefore emphasises the need for creative approaches to providing support, without compromising the independence of ethical committees.

Concluding remarks

Developing countries urgently need research that is of relevance to local healthcare priorities. It is always crucially important that the local social, cultural and economic context is taken into account. The Working Party recognized that it would be impossible to formulate a robust set of rigid guidelines that would be uniformly applicable in all situations. However, the Working Party hopes that the ethical framework established in the Report will be perceived as a significant contribution to international debate on these topics, and that it provides a useful reference for researchers, sponsors, pharmaceutical companies and policy-makers who are designing or conducting research in developing countries.

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Parenteral polymers ▼

In their recent review in *Drug Discovery Today* [1], Hunter and Moghimi comment that synthetic-based polymers have been applied in drug delivery for the past 50 years but there are few examples of these materials being successfully used in the clinic. This is not really surprising. Any pharmaceutical material that is intended for parenteral administration as part of a therapeutic system should exhibit the following basic attributes: (1) non-toxic, (2) non-immunogenic, (3) eliminated, unchanged or metabolized to known products (preferably to endogenous materials).

Whether or not the formulation scientist will choose a synthetic polymer will be dictated by various factors that include the clinical application, the dose of polymer needed and, most importantly, the availability of suitable materials. The decision to use a polymeric material can be a key issue. Most of the polymeric materials available as excipients were not developed specifically for the pharmaceutical industry; some have bizarre origins, such as floor polish components and coating agents. It is, therefore, not unexpected that the injection of such materials into the body could lead to toxic manifestations, to include immunotoxicity. Even macromolecular materials used as plasma expanders have not been without their problems. The adverse effects associated with polyvinyl pyrrolidone and dextrans are well known. Hydroxyethyl starch can be given in large quantities but can have effects on the reticuloendothelial system, especially that in the liver.

Why choose a synthetic polymer?

Normally, polymers are used as excipients or as drug carriers (sometimes via covalent linkage). However, some act as therapeutic agents in their own right (e.g. the polyoxyethylene–polyoxypropylene block copolymer, poloxamer 188, has haemorrheologic and thrombolytic properties).

The physicochemical properties of a polymer itself and the presence of impurities can be of vital importance. The early developments in intravenous

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