July 2000

The ethics of healthcare-related research in developing countries

INVITATION TO COMMENT

The ethical issues raised by developed countries carrying out or sponsoring healthcare-related research in developing countries have received relatively little international attention. Longstanding issues about the ethical acceptability of such research have been highlighted by recent debate about clinical trials of anti-AIDS drugs conducted in developing countries. These trials were designed to see how well shorter courses of a drug called AZT prevented transmission of HIV from HIV-infected pregnant women to their unborn or newborn children.

This recent debate focused on the relatively narrow issue of whether there should be a universal standard of care to which all trial participants should be entitled, irrespective of where they live. However, a much wider range of ethical and social issues is raised by developed countries undertaking or sponsoring healthcare-related research in developing countries. These issues arise because research often involves fundamental conflicts between ethical principles. The duty to conduct good quality research, the need to act in a participant's best interests and the need to respect his or her autonomy can be more difficult to achieve in countries with very limited resources. In developing countries basic healthcare is not widely available and research ethics committees are often underdeveloped or absent.

Two factors are likely to lead to an increase in the amount of healthcare-related research being conducted in developing countries. First, new vaccines and other therapeutic treatments which may be relevant to developing countries are being developed at an increasing rate. Secondly, there is a growing global demand for 'evidence-based medicine'. It can be argued that there is an ethical duty to conduct such research with a view to applying newly emerging scientific knowledge as rapidly as possible. However, it is also very important to ensure that such research is subject to thorough ethical review.

The Nuffield Council on Bioethics has established a Working Party to consider the ethical and social issues posed by healthcare-related research in developing countries. The Working Party includes members with expertise in areas such as medical research, ethics, political theory, regulatory issues, health policy and anthropology. The Working Party's terms of reference and membership can be found at the end of the enclosed consultation document. We have identified those issues which we consider to be significant. Please tell us if we have not covered other important issues.

We would very much welcome your comments on the conduct, assessment and regulation of healthcare-related research in developing countries. We would also value your views on the way in which ethical issues raised by research are being addressed. Further information about the issues is provided in the accompanying consultation document.

We may wish, in the future, to publish some of the views expressed in your response. If you wish your response to be treated in confidence, please make this clear when it is sent to us. The deadline for receipt of comments is **30 November 2000.**

Ms Susan Bull
Secretary to the Working Party

THE NUFFIELD COUNCIL ON BIOETHICS

THE ETHICS OF HEALTHCARE-RELATED RESEARCH IN DEVELOPING COUNTRIES

Consultation Document: July 2000

Introduction

The Nuffield Council on Bioethics, an independent body, has established a Working Party to consider the ethical issues raised by healthcare-related research in developing countries (see **Annex A**). It will report in mid-2001. The Working Party would welcome your comments on the ethical issues raised by healthcare-related research in developing countries and their implications.

This consultation paper discusses some of these ethical issues, particularly when research is sponsored by developed countries and conducted in developing countries. In February 1999, the Council hosted a workshop in London to encourage and stimulate debate in this crucially important area. Following the workshop, the Council published a discussion paper entitled **The ethics of clinical research in developing countries**, which was based on the workshop discussions and background papers. Many of the points described in this consultation paper are discussed in more detail in the discussion paper. If you wish to receive a copy of the discussion paper, it can be obtained free of charge from the Council, or downloaded from our web site (see **Annex B**).

We have posed questions about a number of issues discussed in the text and it would be helpful if you could frame your response around these questions.

Background

There is a wide range of healthcare-related research being conducted in developing countries. Participants can be directly involved in clinical trials of new drugs and vaccines. They may also be involved in research into the natural history of a disease, functioning of the body or behaviour. Epidemiological studies may be aimed at identifying risk factors for diseases and predicting who is most likely to succumb to a disease or how it spreads through a community. These studies may involve participants indirectly, by analysing their medical records or biological samples (such as blood samples) taken at an earlier time.

Many of the most urgent health needs of developing countries could be addressed by improved sanitation, good food and clean water. However, the prevalence of diseases such as HIV/AIDS and malaria means that medical research remains a high priority for many of these countries. However, of the estimated US$ 56 billion spent annually on medical research around the world, at least 90% is spent on the health needs of the richest 10% of the world's population. Therefore just 10% of this research expenditure addresses the needs of 90% of the world's population.

Infectious diseases such as malaria cause 58% of deaths in the poorest 20% of the world's population but only 7% in the richest 20%. Much healthcare research in developing countries concerns infectious diseases, which are either restricted to, or more common in, tropical regions. This kind of research is only of indirect benefit to those countries which sponsor it. However, the emergence of new infections such as HIV, or the emergence of drug-resistant forms of infections such as tuberculosis, can also have a considerable impact on developed countries.

What kind of healthcare-related research is most beneficial to developing countries? How can such research be encouraged?

What harm may be caused by healthcare-related research in developing countries? How may such harms be avoided or lessened?

Issues arising from healthcare-related research

Healthcare-related research is based on two fundamental moral commitments: to improve human welfare by advancing scientific knowledge and understanding of disease; and to preserve and protect the dignity and health interests of the research participant. Such research aims to benefit individual participants and patient groups by identifying and testing improved treatments and to benefit society by making these treatments available. The potential risk of harm to participants has led to widespread agreement that sound ethical standards must be observed in healthcare-related research, no matter where it is undertaken.

A wide range of ethical and social issues, raised by developed countries undertaking or sponsoring healthcare-related research in developing countries, has been under discussion for several years. These issues arise because research often involves fundamental conflicts between ethical principles. These principles include the duty to conduct scientifically sound and reliable research, the need to act in a participant's best interests, and the need to respect a participant's autonomy. These are often more difficult to achieve in poor countries where basic healthcare is not widely available and/or ethical review of research is inadequate.

Healthcare-related research sponsored or undertaken by developed countries in developing countries also raises fundamental questions about distributive justice. The discrepancies in power and wealth between developed and developing countries are reflected in the very different levels of healthcare available.

From your perspective, what are the key ethical issues raised by healthcare-related research in developing countries?

It is widely accepted in healthcare-related research that participants must be respected and their consent sought to participate in a trial. When providing information about a trial to possible participants, problems may arise when translating information into local languages. Some concepts may be hard to explain or may be considered culturally unacceptable. Many cultures will have

their own beliefs about the causes and treatment of illnesses which will differ from the beliefs of the researchers and research sponsors. There may also be difficulties in obtaining appropriate consent from a participant in situations where it is usual for a spouse or local leader to give consent on the participant's behalf.

What do you consider to be the most important cultural issues raised by healthcare-related research in developing countries?

Should we respect cultural practices (such as giving consent on behalf of another) in developing countries when we would not accept them in Western societies?

Questions about whether consent is freely given also raises the issue of inducements. Access to better healthcare and payments may provide powerful incentives to participate in healthcare-related research. In addition, researchers have offered participants money (to reimburse costs), food, photographs and film, and community health interventions. Under these circumstances, it can be difficult to ensure that any consent given is genuine. This problem is also present in developed countries and has attracted considerable attention.[1]

What amounts to an acceptable inducement for a participant to take part in a trial?

When does something become an unacceptable inducement to take part in a trial?

To what extent should people in developing countries be invited to take part in research which may expose them to a risk of harm, and offer them little or no benefit? A person may have little chance of benefiting from research if the intervention being tested is too expensive for their government to purchase. In addition, even if the intervention was made available free of charge, a country may not have the healthcare system needed to deliver the intervention effectively. Guidelines suggest that people in developing countries should not ordinarily be involved in research that could be carried out in developed countries. In addition, how responsive should research be to the health needs and priorities of the community in which it is carried out? [2]

Is it morally acceptable for research to be conducted in a developing country when it could also be conducted in a developed country?

Is it acceptable to allow research in a community that cannot afford the treatment being tested?

---

1 For example see, The Royal College of Physicians of London (1996) **Guidelines on the practice of Ethics Committees in Medical Research involving Human Subjects** (3rd edn) Royal College of Physicians, London.

2 Bankowski Z and Levine RJ (eds) (1993) Ethics and Research on Human Subjects. **International Guidelines. Proceedings of the XXVIth CIOMS Conference**, p ix, CIOMS, Geneva.

What happens once the research is over?

Large-scale trials of interventions in developing countries are frequently associated with improvements in community healthcare during the period of the trial due to better staffing, training and facilities. The support required for this improvement will not ordinarily continue after the trial is over. To what extent healthcare benefits should be sustained after a trial, and by whom, are difficult problems for researchers, sponsors and pharmaceutical companies to solve.

The question of who is responsible for making new drug treatments 'reasonably available' needs to be addressed. There is a danger the research may be limited if the cost implications of successful research are too great for policy makers or research sponsors. The responsibilities of investigators and healthcare providers to the wider population in which research has shown a treatment to be successful raise difficult issues which are common to most if not all countries. These issues are likely to arise with increasing frequency during the coming years as more vaccines, which have the potential to immunise large numbers of people, are tested in developing countries.

If the research has shown an intervention to be successful, is there an ethical responsibility to made sure it is provided after the trial?

Should all who may benefit from a treatment in a country receive it and for how long?

Who should bear the costs? The pharmaceutical sponsors, the public sector sponsors, national government or some other body?

Do researchers have an ethical obligation to undertake long-term surveillance of populations who have received preventive treatments, such as vaccines, to ensure that they are not at increased risk of catching the infectious disease later in life?

Who should be responsible for maintaining an improved standard of care for participants and communities?

Guidelines and regulation

Over the last five decades a succession of international guidelines and declarations have been developed to address the fundamental ethical issues raised by healthcare-related research. The World Medical Association's Declaration of Helsinki [3] and the Council for International Organizations of Medical Sciences (CIOMS) Guidelines are of most relevance to this discussion.

[3] Criminal cases arising from such abuses in Nazi Germany led to the formulation of the Nuremberg Code in 1947. Provisions within this code were endorsed in 1964 by the medical profession in the World Medical Association's (WMA) Declaration of Helsinki.

In collaboration with the World Health Organization (WHO), CIOMS developed its ethical guidelines

> 'to be of use, particularly to developing countries, in defining national policies on the ethics of biomedical research, applying ethical standards in local circumstances, and establishing or redefining adequate mechanisms for ethical review of research involving human subjects'.[4]

Although the CIOMS Guidelines and the Declaration of Helsinki are not legally binding, they are referred to by many regulatory bodies involved in formulating ethical guidelines or regulations for biomedical research.

Although providing general guidance, the Guidelines were not intended to deal with the more detailed aspects of clinical protocols which are sometimes controversial, and are therefore open to different interpretations. For example, in many developing countries there is no prospect at present or in the foreseeable future for widespread anti-HIV drug treatment. It has therefore been argued that studies should be conducted which compare alternative interventions with the current standard local therapy – even if that standard is no treatment. Recently, in developing countries which could not afford full courses of AZT, a controversial trial tested whether a reduced dose of AZT (zidovudine) treatment in HIV-infected pregnant women was better than no treatment at all. The AZT treatment was designed to prevent transmission of HIV from the mother to her child. Influential articles and editorials published in the *New England Journal of Medicine*, and *The Lancet*, alleged that the studies had been unethical and that no patient participating in a trial supported by US funds should be denied the 'standard of care' available in the US. In this debate, both sides cited the Guidelines to support their position. Discussion centred on the question of whether the 'best proven diagnostic and therapeutic method' (Principle II-3 of the Declaration of Helsinki) referred to an international standard or required local resources to be taken into account.

When determining the appropriate standard of care in a clinical trial, should locally available resources be taken into account?

The CIOMS Guidelines advise investigators to submit their proposed work for ethical review in both the country sponsoring the research and the country in which the research is being conducted. However there are no explicit guidelines as to whether either committee has primacy if they hold conflicting opinions. An implication of this is that a single trial design might be judged ethical in one country but not in another. On the one hand, the sponsor needs to be satisfied with the ethics of the research that they are funding. On the other, the host country committee needs to be satisfied that the proposed research takes account of local concerns. Reconciliation of such disagreements may lie in the adoption of a basic set of principles, the observation of which would be necessary for any proposal to be judged ethical, although some committees may be more demanding. The question then is what constitutes a basic principle?

---

4 Bankowski Z and Levine RJ (eds) (1993) Ethics and Research on Human Subjects. International Guidelines. Proceedings of the XXVIth CIOMS Conference, p ix, CIOMS, Geneva.

What are the principles which should guide the conduct of healthcare-related research? Do you consider that the present guidelines and regulations adequately reflect these principles?

International statements concerning the ethics of biomedical research such as the Declaration of Helsinki and CIOMS Guidelines are important and necessary. Yet they pose a number of questions when healthcare-related research in developing countries is being considered. For example, the CIOMS Guidelines have been criticised for failing to address important aspects of healthcare-related research in developing countries, and being complex, insufficiently cross-referenced and impossible to follow in practice.[5] They have been judged as taking too negative a view of medical research, concentrating on the need to avoid harm rather than the need to provide benefits for patients.

Should the CIOMS Guidelines and the Declaration of Helsinki be revised to take greater account of potential benefit as well as possible harm? Should further cross-referencing between these statements be encouraged? Are there specific gaps in the applicability of such guidelines to healthcare-related research in developing countries that need to be addressed? How should areas of ambiguity, such as those concerning appropriate standards of care, be resolved? Are there conditions under which it is impractical or inappropriate to follow the Guidelines in their current form?

Do the present guidelines and regulations provide adequate safeguards and are they sufficiently transparent and accountable? How could they be improved?

There is clearly a very considerable distance between the broadly based principles outlined in international guidelines and the practical issues being considered by local research ethics committees reviewing individual protocols. One appropriate way forward may be to produce 'intermediate' guidelines to link international guidelines and issues considered by research ethics committees. Such intermediate guidelines could be generated by national or international bodies.

How should conflicts about the interpretation of the principles in international guidelines be resolved?

Implementation of guidelines

While the content of the Guidelines is important, equally important is awareness of their existence and the capacity to implement them. Many researchers in both developed and developing countries are unaware of either the existence of the relevant guidelines and declarations, or their contents. The CIOMS Guidelines and the Helsinki Declaration cannot be effective unless accompanied by the

---

[5] For example, the CIOMS Guidelines require that initial studies of drugs and vaccines must be conducted in the country which develops the drug, to avoid the risk of initial trials being conducted in countries without appropriate ethical review. This may raise difficulties where developed countries wish to conduct a trial of therapies which are going to be used primarily in developing countries.

training and resources required for their effective implementation in developing countries.

In addition to the need to establish the most effective way to disseminate guidelines among researchers, concerns are often raised about the effectiveness of local research ethics committees. The very countries likely to be most vulnerable to unethical or exploitative healthcare-related research may be those with the least developed systems to review such research. Several developing countries do not yet have research ethics committees and, even where they are established, the pool of trained and experienced personnel is often very limited. This may mean that some individuals review proposals in which they may have a material interest.

The implementation of guidelines in developing countries therefore raises a number of issues:

- Before research ethics can be taken seriously, there must be 'ownership' of the general principles of medical ethics amongst the medical and research community.
- Individuals may lack the training or expertise to deal with the problems that arise in applying any set of guidelines. To achieve this, funding to establish and operate ethics committees is needed.
- Ethics committees may be physically, socially, economically or culturally removed from the population or community which is to be studied. A local research ethics committee should be constituted so that it understands the local community's customs and traditions.

Are local or national research ethics committees the best means of protecting the interests of participants in developing countries?

What is the most effective way to involve local investigators, other health professionals, pharmaceutical companies, government agencies and other research funders in the development of research protocols so that such research can offer most benefit to the community?

Should additional international regulatory agencies be established to oversee the implementation of agreed guidelines and the resolution of disputes?

Annex A

Membership of the Working Party

Professor Sir Kenneth Calman (Chairman)
Vice-Chancellor and Warden, University of Durham and member of Nuffield Council on Bioethics

Dr Fred Binka
Navrongo Health Research Centre and Ghana School of Public Health

Professor Michael Elves
Former Director, Office of Scientific and Educational Affairs, Glaxo Wellcome plc

Professor V I Mathan
Division Director for Laboratory Sciences Division, International Centre for Diarrhoeal Disease Research, Dhaka

Professor Keith McAdam,
Director, MRC Laboratories, Fajara, The Gambia

Dr Anne McLaren,
Wellcome/CRC Institute, Cambridge

Professor Bhiku Parekh,
Professor of Political Theory, University of Hull

Professor David Parkin,
Professor of Social Anthropology, All Souls College, Oxford

Professor Catherine Peckham CBE,
Professor of Epidemiology, Institute of Child Health, University College London and member of Nuffield Council on Bioethics

Professor Povl Riis,
Copenhagan Ministry of Science

Professor Nelson Sewankambo,
Dean, Faculty of Medicine, Makerere University, Kampala, Uganda

Mrs Shahwar Sadeque,
Educational & ICT Consultant

Professor Peter Smith,
Head of Department of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine

Dr Fabio Zicker,
Co-ordinator, Research Capacity Strengthening and Tropical Diseases Research Programme, World Health Organization

Annex B

The Council's discussion paper entitled **The ethics of clinical research in developing countries** can be downloaded at
http://www.nuffieldfoundation.org/bioethics/publication/download.html

Paper copies are also available to order.

For further information please contact:
Yvonne Melia
Nuffield Council on Bioethics
28 Bedford Square
London WC1B 3EG
Tel: 020 7681 9625
Fax: 020 7637 1712
Email: ymelia@nuffieldfoundation.org