

**Published by
Nuffield Council on Bioethics
28 Bedford Square
London WC1B 3EG**

**Telephone: 0171 681 9619
Fax: 0171 637 1712
Email: bioethics@nuffieldfoundation.org
Website: <http://www.nuffieldfoundation.org>**

**ISBN 0 9522701 5 3
October 1999**

© Nuffield Council on Bioethics 1999

All rights reserved. Apart from fair dealing for the purpose of private study, research, criticism or review, no part of the publication may be produced, stored in a retrieval system or transmitted in any form, or by any means, without prior permission of the copyright owners.

Printed by Henry Ling
23 High Street
Dorchester
Dorset DT1 1HD

Cover designed by Geoffrey Wadsley

The ethics of clinical research in developing countries

**NUFFIELD
COUNCIL^{ON}
BIOETHICS**

Nuffield Council on Bioethics

Professor Ian Kennedy (Chairman)

Professor Martin Bobrow CBE

Revd Professor Duncan Forrester

Professor Brian Heap CBE FRS

Lady Sonia Hornby

Dr Anne McLaren DBE FRS

Dr Brian Newbould

Mr Derek Osborn CB

Professor Martin Raff

Nick Ross

Professor Dame Margaret Turner-Warwick DBE

Professor Albert Weale

Secretariat

Dr Sandy Thomas (Director)

Ms Susan Bull

Ms Julia Fox

Ms Yvonne Melia

The terms of reference are as follows:

- 1 to identify and define ethical questions raised by recent advances in biological and medical research in order to respond to, and to anticipate, public concern;
- 2 to make arrangements for examining and reporting on such questions with a view to promoting public understanding and discussion; this may lead, where needed, to the formulation of new guidelines by the appropriate regulatory or other body;
- 3 in the light of the outcome of its work, to publish reports; and to make representations, as the Council may judge appropriate.

**The Nuffield Council on Bioethics is funded jointly by
the Medical Research Council, the Nuffield Foundation and
the Wellcome Trust**

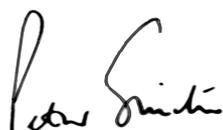
Foreword

The Nuffield Council on Bioethics is an independent body which was established in 1991 to examine the ethical issues arising from developments in biomedicine and biology with a view to both assisting in the formation of public policy and in fostering public understanding. Once the Council has identified an area of major ethical concern, it establishes a multidisciplinary Working Party, whose members have the relevant expertise to examine and report on the area. It has published five major reports dealing with the ethical issues associated with genetic screening, ownership of human tissue, xenotransplantation, genetics and mental disorders, and genetically modified crops.

In 1998 the Council determined that it would be timely to discuss the ethical issues arising from the conduct of clinical research in developing countries. In particular, those ethical issues surrounding clinical research in developing countries that is sponsored by agencies or companies in developed countries, or is carried out in collaboration with scientists from developed countries, have received relatively little international attention. Some of the issues were highlighted in the recent debate about large-scale trials conducted in developing countries to test treatment with zidovudine (AZT) to prevent perinatal transmission of HIV. The ethical issues raised in that debate, such as whether there should be a universal standard of care to which trial participants should be entitled, irrespective of their country of residence, were not new nor were they confined to the trials being discussed. Indeed, many of the concerns about clinical research conducted in developing countries also apply to research being conducted in developed countries. They tend, however, to be exacerbated when only very limited resources are available, as may be the case in developing countries.

Rapid developments in biotechnology have accelerated the rate of development of new vaccines and other preventative and curative treatments which may have great relevance for disease control in developing countries. There has been a parallel increase in global demand for 'evidence-based' medicine, aimed at restricting the introduction of new interventions into disease-control programmes until evidence of efficacy is properly established. These dual developments are likely to lead to an increase in the number of studies of efficacy and effectiveness in developing countries. Many of these studies will be funded, at least in part, by sponsors from the richer countries of the world. While it can be argued that there is an ethical imperative to conduct research with a view to applying newly emerging scientific knowledge for disease control as rapidly as possible, it is also very important to ensure that such research is subject to thorough ethical review.

In February 1999 the Council hosted a workshop in London to encourage and stimulate debate in this crucially important area. The Workshop was attended by 30 leading experts from 18 countries and was sponsored by the UK Medical Research Council, the Wellcome Trust and the UK Department For International Development. This paper is based on Workshop discussions and background papers. It is being followed by a Working Party set up by the Council and to be chaired by Sir Kenneth Calman, which will report early in 2001.



Professor Peter Smith
Workshop Steering Group

Acknowledgements

The Council wishes to thank Dr Imogen Evans, Ms Marion Kelly, Dr Richard Lane and Professor Peter Smith of the Workshop Steering Group for their help in planning the Workshop on the ethics of clinical research in developing countries and for their assistance in the preparation of this Discussion Paper. Their expertise has been invaluable. The Council would also like to thank Dr Angus Nicoll, Dr Charles Gilks, Dr Bertie Squire, Professor T Jacob John, Professor Keith McAdam, Professor Ruth Macklin, Professor Michael Farthing, Dr Alwyn Mwinga and Professor Brian Greenwood for preparing the background papers for the Workshop. The background papers provided an excellent basis for discussion and much of the material in them has been incorporated into this Discussion Paper. The Council is also very grateful to Professor Janet Darbyshire, Mrs Claire Foster, Dr Jane Kengeya-Kayondo, Professor Kevin Marsh, Baroness Onora O'Neill and Dr John Porter, who all reviewed an earlier version of the paper. Their comments contained both far-reaching and detailed criticisms to which we have sought to respond. We would like to thank all those who attended the Workshop for their wide-ranging and thoughtful contributions to the discussion. The Council is particularly grateful to Julia Fox and Susan Bull for organising the Workshop. Finally, the Council wishes to thank the Department for International Development, the Medical Research Council and the Wellcome Trust for their generosity in sponsoring the Workshop.

Workshop Steering Group

Dr Imogen Evans

Research Strategy Manager for Clinical Sciences, The Medical Research Council, London, UK

Ms Marion Kelly

Research Specialist, Department for International Development, London, UK

Dr Richard Lane

Head of International Programmes, The Wellcome Trust, London, UK

Professor Peter Smith

Head of Department of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, UK

Dr Sandy Thomas

Director, Nuffield Council on Bioethics

Dr Rachel Bartlett (until August 1998)

Ms Susan Bull (from October 1998)
Deputy Director, Nuffield Council on Bioethics

Workshop delegates

Professor Janet Darbyshire

Head of MRC HIV Clinical Trials Centre, University College London Medical School, London, UK

Dr Soledad Diaz

Consultorio De Plantification Familiar, Institute Chileno de Medicina Reproductiva, Santiago, Chile

Mr Robert Eiis

Assistant Director of International Science Policy & Analysis, Fogarty International Centre, National Institutes of Health, Maryland, USA

Dr Michael Elves

Former Director, Office of Scientific and Educational Affairs, Glaxo Wellcome plc, UK

Professor Michael Farthing

*Director, Digestive Diseases Research Centre
St Bartholomew's and The Royal London School of Medicine and Dentistry, London, UK*

Revd Professor Duncan Forrester

*Dean, Faculty of Divinity, The University of Edinburgh, Edinburgh, UK
Member of the Nuffield Council on Bioethics*

Dr Charles Gilks

Professor of Tropical Medicine, Liverpool School of Tropical Medicine, Liverpool, UK

Professor Brian Greenwood

*Professor of Communicable Diseases,
Clinical Research Unit, London School of Hygiene and Tropical Medicine, London, UK*

Professor T Jacob John

Department of Clinical Virology, Christian Medical College and Hospital, Velore, India

Professor Salim Abdool Karim

Director, CERSA, Medical Research Council, Durban, South Africa

Dr Jane Kengeya-Kayondo

*Manager, Task Force on Malaria Home Management,
Special Programme for Research & Training in Tropical Diseases, WHO, Geneva,
Switzerland*

Professor Wen Kilama

*Chairman cum Co-ordinator, African Malaria Vaccine Testing Network, Dar es Salaam,
Tanzania*

Professor Adetokunbo Lucas

Adjunct Professor of International Health, Harvard University, Boston, USA

Professor Ruth Macklin

*Department of Epidemiology & Social Medicine, Albert Einstein College of Medicine,
New York, USA*

Professor Kevin Marsh

KEMRI, Centre for Geographic Medicine Research – Coast, Kilifi, Kenya

Professor Keith McAdam

Director MRC Unit, MRC Laboratories, Fajara, The Gambia

Professor Malcolm Molyneux

Director, Wellcome Trust Centre and Malaria Project, Malawi

Dr Alwyn Mwinga

Project Co-ordinator, UNZA-UCLMS Project, Lusaka, Zambia

Dr Angus Nicoll

*Head of HIV & STD Division, Communicable Disease Surveillance Centre,
Public Health Laboratory Service, London, UK*

Baroness Onora O'Neill

Principal, Newnham College, University of Cambridge, Cambridge, UK

Professor Catherine Peckham

*Head of Department of Epidemiology & Public Health
Institute of Child Health, University College London Medical School, London, UK*

Professor Povl Riis

Copenhagen Ministry of Science, Copenhagen, Denmark

Dr Pratap Singhasivanon

*Head of Department of Tropical Hygiene and Director of Vaccine Trial Centre,
Mahidol University, Bangkok, Thailand*

Professor Rachel Snow

Department of Tropical Medicine and Public Health, University of Heidelberg, Germany

Mr Hugh Whittall

*Scientific Officer, Directorate of Life Sciences, European Commission DGXII, Brussels,
Belgium*

Dr Jimmy Whitworth

*Team Leader, MRC Research Programme on AIDS, Uganda Virus Research Institute,
Entebbe, Uganda*

Executive Summary

The ethical acceptability of developed countries' supporting or undertaking research in developing countries has been debated for many years. The ethical issues have recently been highlighted by controversy surrounding large scale trials conducted in developing countries to see whether zidovudine (AZT) treatment for HIV-infected women prevented perinatal transmission of HIV. The ensuing debate has focused attention on the relatively narrow issue of standards of care in clinical trials in developing countries. However, this paper, based on discussions which took place at an international Nuffield Council on Bioethics workshop in February 1999, draws attention to the fact that a much wider range of ethical and social issues need to be addressed. The duty to conduct scientifically sound research, the need to act in the patient's best interests and the need to respect the patient's autonomy are fundamental to all clinical research but may be more difficult to achieve in poor countries where basic healthcare is not widely available. Questions about justice are also particularly relevant where limited resources mean that effective treatments may be unaffordable.

In view of the potential risk of harm in clinical research, sound ethical standards must be observed, irrespective of the geographic and economic setting in which such research is undertaken. Unfortunately the mechanisms and procedures for ethical review in some developing countries are under-developed. This paper suggests that while the Declaration of Helsinki and international biomedical guidelines are both necessary and useful, they have weaknesses which need to be addressed. Furthermore, such guidance can only facilitate protection of the interests of trial participants if training and resources are available for its interpretation and implementation.

A range of ethical and social issues is highlighted which need to be addressed by research sponsors, intending collaborators and relevant authorities in poor countries. These include the relevance of the research to the country's health needs, the availability of effective treatments after research is completed, the need to respect cultural traditions when conducting research and issues relating to consent.

There is clearly a very considerable distance between the broadly based principles outlined in international guidance and the practical issues being considered by local research ethics committees reviewing individual protocols. One way forward would be to produce 'intermediate' guidelines to link these two levels of ethical assessment. Those international bodies undertaking inquiries on this topic have acknowledged the importance of bringing their studies together to create coherent guidance.

Introduction

- 1 Longstanding issues about the ethical acceptability of developed countries' supporting or undertaking research in developing countries have been highlighted by recent debate about large-scale trials conducted in developing countries testing zidovudine (AZT) treatment for HIV-infected pregnant women to prevent perinatal transmission of HIV. These issues were raised in September 1997 in a paper by Lurie and Wolfe and an editorial by Angell published in the *New England Journal of Medicine*,¹ together with an editorial on ethics in *The Lancet*,² alleging that the studies had been unethical (see Appendix). Lurie and Wolfe's article and Angell's editorial argued that no patient participating in a trial supported by US funds should be denied the 'standard of care' available in the US (paragraphs 25-26 and Appendix). To support this argument the authors cited the Declaration of Helsinki, which states that trial participants 'should be assured of the best proven diagnostic and therapeutic method' (Principle II-3), and the CIOMS (Council for International Organizations of Medical Sciences) Guidelines. It was also argued that any trial sponsored from abroad should be judged ethically acceptable in both host and source countries.
- 2 The debate about the evaluation of methods to prevent perinatal transmission of HIV/AIDS has focused discussion on the relatively narrow issue of standards of care in clinical trials in developing countries. In fact, a much wider range of ethical and social issues raised by developed countries undertaking or sponsoring clinical research in developing countries has been under discussion for several years.³ These issues arise because research often involves fundamental conflicts between ethical principles. The duty to conduct scientifically sound and reliable research, the need to act in a participant's best interests, and the need to respect his or her autonomy are often more difficult to achieve in poor countries where basic healthcare is not widely available and research ethics committees are underdeveloped or absent. In almost all circumstances the researchers' knowledge about the research being conducted will be greater than the participants' but this disparity tends to be greater when research is conducted in developing countries.
- 3 The question of compensation to persons injured or placed at increased risk as a result of research may also be more difficult to resolve when the sponsors are from a developed country. This issue has arisen recently during the course of a trial of the malaria vaccine SPf66 in Gambian infants. Analysis of follow-up data from a pilot trial which was obtained after the main trial had started suggested that vaccinated children were *more* at risk of malaria than children in the control group.⁴ In this case, the UK Medical Research Council (MRC) provided additional funds so that surveillance of trial

1 Lurie P and Wolfe SM (1997) Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries, **New England Journal of Medicine**, 337: 883–885; Angell M (1997) The ethics of clinical research in the third world, **New England Journal of Medicine**, 337: 847–849.

2 Editorial (1997) The ethics industry, **The Lancet**, 350: 897.

3 The definition of clinical research used by the Medical Research Council is 'research primarily based on patients or ex-patients and designed to answer a question about disease (aetiology, concomitants, diagnosis, prevention, outcome or treatment). In addition to direct clinical examination, it includes study of blood, biopsy material or post-mortem tissue deriving from the individuals concerned, and of normal subjects where such study relates to a disease process being investigated. The definition includes clinical trials, and of course much other work on the clinical characterisation of disease or ill health.'

4 A control group contains participants who remain untreated or who are treated with drugs/methods currently used in clinical practice. The results from this group are compared with those of another group of individuals who are given the novel treatment which is being tested.

The ethics of clinical research in developing countries

participants could be increased and facilities for the treatment of malaria in the study area improved. Surveillance was also continued for two years after the trial had been completed. Fortunately, although vaccine recipients were not protected from malaria, they were not found to be at any enhanced risk of infection on prolonged surveillance.

- 4 Where a successful intervention from a clinical trial is designed to prevent an illness arising only in the early period of life,⁵ the investigators and their sponsors may have no more responsibility to trial participants once the participants are beyond the age of risk for the disease under study. However, this will not be the case with infectious diseases, where induced immunity is not permanent and prevention of infection in infancy or early childhood may merely postpone serious adverse outcomes until the child is older. In some parts of the developing world, *Haemophilus influenzae* type b (Hib) infections mainly feature in the first year of life. Following participants in a Hib vaccination trial beyond early childhood might be important to assess any increase in risk from infection in later childhood, an approach which is being adopted in some developed countries such as the UK.
- 5 Risk of severe infection following early preventive measures is also a concern in the case of malaria, where the development of natural immunity follows repeated exposure to the disease. Early interventions may increase the likelihood of severe infection in later childhood and rates of morbidity or mortality. Several large field trials have shown that insecticide-treated bednets and curtains reduce overall mortality in young African children by 20–30%. There is a theoretical possibility that, following this early protection, such children may be at increased risk of contracting malaria in later childhood, but it is still unclear whether this will in fact occur. These two examples raise questions about the responsibilities of developed country researchers to participants in developing countries once a trial is completed. In particular, do investigators have an ethical obligation to undertake long-term surveillance of populations who have received preventive treatment? It could be argued that long-term surveillance should be an essential component of all Stage IV clinical trials.
- 6 The responsibilities of investigators to the wider population in which an intervention has been shown to be successful raises difficult issues which are common to most if not all countries. However, they are particularly hard to resolve in some parts of the developing world where there may be substantial logistical and financial constraints impeding the adoption of new treatments or interventions on a population-wide basis. For example, although a successful national trial of insecticide-treated bednets in the Gambia reduced overall child mortality by approximately 30%, it was decided by the investigators, sponsors and the Ministry of Health that cost recovery for the insecticide would have to be introduced after the trial because the Ministry could not afford to provide free insecticide indefinitely. Introduction of cost recovery led to a reduction in the number of young children sleeping under an insecticide-treated net from around 70% to 20%.⁶
- 7 It should also be borne in mind that while interventions may initially be too costly to implement, costs may subsequently fall. A hepatitis vaccine, used successfully in a trial in the Gambia, was initially too expensive to adopt at over US\$20 per dose. Since then, the price has decreased greatly and the Gambian government has been able to

5 For example, a non-recurring nutritional deficiency which occurs during the first two years of life.

6 Cham K, Olaleye B, D'Alessandro U, Aikins M, Cham B, Main N, *et al.* (1997) The impact of charging for insecticide on the Gambian National Impregnated Bednet Programme, **Health Policy and Planning**, 12: 240–247.

maintain a vaccination programme.⁷ In another example, Ivermectin, originally developed for treating cattle and other animals for worm infestation, was subsequently found to be also highly effective in humans, but was too expensive for developing country use. However, the pharmaceutical company which produced the drug decided to provide it at no cost.

Background

- 8 Although many of the urgent health needs of developing countries could be addressed by improved sanitation, adequate nutrition and clean water, 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 by the global community, at least 90% is spent on the health needs of the richest 10% of the world's population. Only 10% of this research expenditure therefore addresses the needs of 90% of the world's population.⁸
- 9 Infectious diseases cause 58% of deaths in the poorest 20% of the world's population but only 7% in the richest 20%. Much clinical research in developing countries concerns infectious diseases such as malaria, which are either geographically restricted to tropical regions or are more frequent in such regions. This kind of research is only of indirect benefit to developed countries which sponsor it. However, the emergence of new infections such as HIV, or the development of drug-resistant forms of infections, such as tuberculosis, can also have a considerable impact on developed countries. Increasing amounts of international travel and the movement of refugees has led to these diseases being more widely distributed across the globe. The predicted rise in non-communicable diseases in developing countries (for example cerebrovascular disease and ischaemic heart disease), which currently cause 85% of the mortality in the richest 20% of the world's population but only 23% in the poorest 20%, will increase the range of clinical studies in many parts of the developing world.
- 10 The spectrum of research involving human subjects conducted in developing countries is extremely wide. It can involve direct contact with participants in clinical trials of new drugs, vaccines and diagnostics, or improved clinical management strategies. Participants can also be directly involved in basic clinical research studies on the natural history of a disease, the functioning of the body or on behaviour. Epidemiological studies may be aimed at identifying risk factors and predicting those most likely to succumb to a disease or at determining how a disease spreads through a community. These studies may involve individuals directly or indirectly, for example through analysis of their clinical records or biological samples taken at an earlier time.
- 11 There is a considerable potential for ethical disputes to arise where clinical research, supported by developed countries, takes place in developing countries. Research partnerships where one partner is dominant in terms of funding and organisation may lead to ethical standards being compromised and the possible exploitation of both researchers and research participants. The problem is exacerbated by the fact that potential research participants in some developing countries, whether patients or healthy volunteers, will often be more vulnerable to exploitation than those living in

7 Greenwood B (1999) After the trial is over, **Nuffield Council on Bioethics Workshop on the Ethical Issues of Clinical Research in Developing Countries**, 21–23 February 1999, London.

8 *Ad hoc* Committee on Health Research Relating to Future Intervention Options (1996) **Investing in Health Research and Development**, World Health Organization, Geneva (unpublished document TDR/GEN/96.1).

wealthy countries for a variety of reasons. These include limited access to basic healthcare, the difficulties of implementing guidance set out in international guidelines in local circumstances, consent procedures where cultural norms may conflict with developed country notions of autonomy and a relative lack of familiarity with developed country concepts of research and research procedures. The purpose of this paper is to identify and discuss these issues, giving particular emphasis to the adequacy and implementation of international guidelines, consent to participate in clinical research, issues raised by HIV/AIDS vaccine trials and healthcare issues arising at the completion of the trial.

General ethical issues

- 12 Clinical research involving human participants is premised 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. Clinical research aims to benefit individual participants and patient groups through the identification and testing of improved therapeutic 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 clinical research, irrespective of the geographic and economic setting in which it is undertaken. Clinical 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 widely differing availability of healthcare resources and the quality of healthcare provision.
- 13 To what extent should individuals in developing countries be invited to take part in research which may expose them, and the populations from which they are drawn, to a possible risk of harm, yet offer them little or no direct benefit? CIOMS Guideline 8 (see paragraphs 20–24) states that persons in underdeveloped communities should not ordinarily be involved in research that could be carried out in developed communities and that research should be responsive to the health needs and priorities of the community in which it is carried out. Such guidance is particularly relevant to research in developing communities where poorer, more vulnerable individuals may be participants in research that may primarily benefit better-educated and financially privileged social groups, either in their own country or even in the developed world. Is it acceptable to allow research in a community that is unlikely to be able to benefit in the longer term from an intervention because, for example, of its high cost, despite the fact that in some cases costs may decrease over time?
- 14 In medical care, ethical requirements are integral to the health provider's duty of care to act in their patients' best interests and the need to respect patient autonomy by seeking consent to treatment from patients or by providing special protection for patients who are not competent to consent. However, in medical research, in addition to their responsibilities to participants in a study, researchers have a responsibility to the wider community. This dual responsibility could provide reasons for a researcher to make different choices about the adoption of clinical measures than they would have made if the participant's best interests and autonomy were their only concerns. For example, in clinical trials, healthcare workers may administer placebos or take blood

samples for tests which are not designed to benefit participants directly.⁹ The potential conflict is resolved by seeking to ensure that, in serving the interests of society, the interests of the participant are not harmed: hence the need for consent to research.

- 15 It is widely accepted in clinical research that participants must be respected and their consent sought to participate in a trial. There may be problems of language and some concepts may be difficult to explain or may be considered culturally unacceptable. There may also be difficulties in obtaining appropriate consent from a participant in situations where it is customary for a spouse or community to give consent on the participant's behalf. How can these cultural traditions be respected or accommodated when they lead to decisions or processes which would be considered unacceptable in the sponsoring country? Questions about whether consent is freely given also raise the issue of inducements. Access to better healthcare and payment may provide powerful incentives to participate in clinical research. Under these circumstances, it can be difficult to ensure that consent procedures are genuine and legitimating. That said, this problem is also present in developed countries and has attracted considerable attention.¹⁰
- 16 Ethical review of research provides a safeguard for the participant. However, mechanisms and procedures for local ethical review in some developing countries are under-developed. The very countries likely to be most vulnerable to unethical or exploitative clinical research may be those with the least developed systems to review such research. A lack of appropriately trained people and resources may lead to problems in establishing ethics committees. As a result it can be very difficult to obtain appropriate or even valid ethical review of clinical research proposals in some areas. Where appropriate research ethics committees are established in developing countries, they may reach different conclusions about the acceptability of individual research protocols from the committees in the developed countries which are sponsoring the research. Such conflicts between the views of the committees in the participating countries raise further problems (see paragraph 26).
- 17 What happens after the clinical trial is over? The quality of healthcare available to a trial community will probably decline at the end of a trial. Often, large-scale trials of interventions in developing countries are associated with improvements in community healthcare during the period of the trial due to better staffing and facilities. The support required for the improvement will not ordinarily continue after the trial is over. Is there an ethical obligation on some body to maintain an improved standard of care for participants after the trial? If the trial showed that the intervention being tested was successful, is there an obligation to continue to provide such an intervention to participants? Does any such responsibility lie solely with the health authorities or also with the investigators, sponsors and pharmaceutical companies involved in the trial? 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.

9 A placebo is a treatment known to be without a clinical effect, usually used as a control to be compared against the potentially effective substance or method which is being subjected to clinical trial.

10 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.

Are the existing guidelines good enough?

- 18 During this century, unethical clinical research has harmed research participants in a number of countries. Criminal cases arising from such abuses in Nazi Germany led to the formulation of the Nuremberg Code in 1947.¹¹ Provisions within this code were endorsed in 1964 by the medical profession in the World Medical Association's (WMA) Declaration of Helsinki.¹² Because clinical research involving human participants raises fundamental ethical issues, a succession of international guidelines and declarations concerning such research has been developed during the last five decades (Table 1). These documents demonstrate a trend towards making more explicit the ethical considerations which should be taken into account if research on human beings is to be ethically acceptable.
- 19 There are three main sets of guidelines which are routinely consulted concerning the ethical conduct of research. All three draw on the Declaration of Helsinki. The Guidance on Good Clinical Practice, was created by the International Conference on Harmonisation (ICH) and Committee for Proprietary Medicinal Products for the pharmaceutical industry, and provides unified technical standards for clinical trials, so that data generated are mutually acceptable to regulatory authorities in the European Union, Japan and the United States. The Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products from the World Health Organization are brief and practical and outline basic prerequisites for the ethical conduct of research.
- 20 The Council for International Organizations of Medical Sciences (CIOMS) Guidelines (the Guidelines) are of most relevance to this paper. In collaboration with the World Health Organization (WHO), CIOMS developed this ethical guidance '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'.¹³ These Guidelines draw on the Nuremberg Code, the Declaration of Helsinki and the Universal Declaration of Human Rights (see Table 1). Most of the Guidelines have some relevance to the ethics of clinical research in developing countries, with Guideline 8 specifically focusing on this area (Table 2). The Guidelines and the Declaration of Helsinki have no inherent legal authority but are referred to by many regulatory bodies involved in formulating ethical guidelines or regulations for biomedical research.
- 21 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 the debate concerning the 'standard of care' in the perinatal HIV transmission studies, both sides cited the Guidelines to support their position (see Appendix). Debate centred on the question of

11 The Nuremberg Code (1947) arose from a trial at the end of the Second World War by the US Military Tribunal of 23 Germans accused of war crimes and crimes against humanity for their role in conducting unethical medical experiments on concentration camp inmates. The trial led to the production of a code which defined 'permissible medical experiments'. The code focuses on the principles of voluntary consent and assured protection from physical and mental suffering of human subjects participating in research which are regarded as essential.

12 A further revision of the Declaration of Helsinki is currently under discussion.

13 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.

The ethics of clinical research in developing countries

whether the 'best proven diagnostic and therapeutic method' (Principle II-3 of the Declaration of Helsinki) refers to an international standard or should take local resource considerations into account. To what extent should the principles of minimising risk be tempered by practical resource considerations? An additional 'layer' of guidance, intermediate between the 'big ethics' of international guidelines and the 'little ethics' of local ethics research committees may be needed.

- 22 The Guidelines also fail to address specific but important aspects of clinical research in developing countries. For example, Guideline 9, which concerns epidemiological studies does not explicitly refer to community trials or refer to the extensive literature on these.¹⁴ In addition, the Guidelines have been criticised for being complex,

Table 1: Chronology of guidelines concerned with biomedical research

Year	Document	Authority
1947	Nuremberg Code	
1948	Universal Declaration of Human Rights	United Nations General Assembly
1964	Declaration of Helsinki (1)	World Medical Association ¹⁵
1966	International Covenant on Civil and Political Rights	United Nations General Assembly
1975	Declaration of Helsinki (2) – Tokyo	World Medical Association
1983	Declaration of Helsinki (3) – Venice	World Medical Association
1989	Declaration of Helsinki (4) - Hong Kong	World Medical Association
1991	International Guidelines for Ethical Review of Epidemiological Studies	CIOMS / WHO
1993	International Ethical Guidelines for Biomedical Research Involving Human Subjects	CIOMS / WHO
1995	Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products	WHO
1996	Declaration of Helsinki (5) - South Africa	World Medical Association
1996	International Conference on Harmonisation (ICH) Guidance on Good Clinical Practice	CPMP/ICH

14 Community trials are trials of interventions that are applied to populations rather than to individuals. The populations may be small, such as part of a village, or large, for example a whole sector of a region.

15 This Declaration provides recommendations to guide physicians in biomedical research involving human participants. The third of the four revisions (Hong Kong, 1989) was incorporated in the CIOMS Guidelines.

TABLE 2: The International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS and WHO, 1993).

Guideline	Subject
Guideline 1:	Individual informed consent
Guideline 2:	Essential information for prospective research subjects
Guideline 3:	Obligations of investigators regarding informed consent
Guideline 4:	Inducement to participate
Guideline 5:	Research involving children
Guideline 6:	Research involving persons with mental or behavioural disorders
Guideline 7:	Research involving prisoners
Guideline 8:	Research involving subjects in underdeveloped communities
Guideline 9:	Informed consent in epidemiological studies
Guideline 10:	Equitable distribution of burdens and benefits
Guideline 11:	Selection of pregnant or nursing (breastfeeding) women as research subjects
Guideline 12:	Safeguarding confidentiality
Guideline 13:	Right of subjects to compensation
Guideline 14:	Constitution and responsibilities of ethical review committees
Guideline 15:	Obligations of sponsoring and host countries

insufficiently cross-referenced and lacking specificity. They have also 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. It has therefore been suggested that more emphasis should be given to the necessity of developing an empirical body of knowledge upon which medical decisions can be based.¹⁶

- 23 Some of the Guidelines may be impossible to follow in practice. For example, the CIOMS commentary on Guideline 8 states 'As a general rule the sponsoring agency should ensure that, at the completion of successful testing, any product developed would be made reasonably available to the inhabitants of the underdeveloped community in which the research was carried out'. Such research is generally undertaken without any guarantee that the treatment in question would be provided to the community from which the participants are drawn in the event of a positive

¹⁶ Nicoll A (1999) Are existing guidelines good enough? **Nuffield Council on Bioethics Workshop on the Ethical Issues of Clinical Research in Developing Countries**, 21–23 February 1999, London.

outcome. The Guidelines also require that Phase I drug studies and Phase I and II vaccine studies 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 such as anti-malarials, which are going to be used primarily in developing countries.¹⁷

- 24 The Guidelines need to be revisited in the light of these weaknesses. A clarification of the relationship between the CIOMS Guidelines and the Declaration of Helsinki is needed to determine which has primacy when there are apparent conflicts between the two. While the content of the Guidelines is important, equally important is awareness of their existence and the capacity to implement them (see paragraphs 28–34 for a further discussion of capacity building). Many researchers in both developed and developing countries are unaware of either the existence of the relevant guidelines and declarations, or their contents. There is a need to establish the most effective way to disseminate and publicise such guidelines and declarations among researchers.

The application of the Guidelines in externally sponsored trials in developing countries

- 25 The articles by Lurie and Wolfe, and Angell (see paragraph 1 and Appendix) argued that no patient participating in a trial supported by US funds should be denied the 'standard of care' available in the US. They cited in support of this argument Principle II-3 of the Declaration of Helsinki which states trial participants 'should be assured of the best proven and diagnostic method'. Such an interpretation of the Principle would exclude almost all controlled trials whether the control group received no treatment (with or without a placebo) or a comparison treatment which was less than the optimal treatment available in a developed country. However, the introduction to the CIOMS Guidelines states that their purpose is to indicate how the ethical principles set out in the Declaration of Helsinki 'could be effectively applied, particularly in developing countries given their socio-economic circumstances, laws, regulations and executive and administrative arrangements'. Furthermore, the Guidelines state that research in developing countries needs to be 'responsive to the health needs and the priorities of the community in which it is to be carried out'.¹⁸
- 26 Lurie and Wolfe, and Angell, also argued that any trial sponsored from abroad should be judged ethically acceptable in both host and source countries. The CIOMS Guidelines state that 'the ethical standards applied should be no less exacting than they would be in a case of research carried out in that [the source] country'.¹⁹ Although the Guidelines advise investigators to submit their proposed work for ethical review in both countries, there is no explicit guidance as to whether either committee has primacy if they hold conflicting opinions.²⁰ However, the CIOMS Guidelines go on to

17 A further problem is raised by trials which test the efficacy of interventions such as anti-tuberculosis drugs in developing rather than developed countries because there are larger numbers of patients available. These drugs will often be too costly for patients in developing countries or their delivery may be impractical in the context of local infrastructure.

18 CIOMS in collaboration with WHO (1993) **International Ethical Guidelines for Biomedical Research Involving Human Subjects**, Guideline 8: p. 25, CIOMS, Geneva.

19 CIOMS in collaboration with WHO (1993) Guideline 15: p 43.

20 Guideline 15 states that committees in external sponsoring countries have a special responsibility to 'determine whether the scientific methods are sound and suitable for the aims of the research, whether the drugs, vaccines or devices to be studied meet adequate standards of safety, whether there is sound justification for conducting the research in the host country rather than in the country of the external sponsoring agency, and that the proposed research does not in principle violate the ethical standards of the

The ethics of clinical research in developing countries

indicate that the host country's ethics committee has a 'special responsibility' on matters of detail of a trial, such as the acceptability of plans to obtain informed consent, while committees in the sponsoring body need only to be satisfied that the trial conforms broadly to the ethical standards prevailing in their own country. Such clauses recognise the host country committee's 'better understanding of the cultural and moral values of the population in which the research is proposed to be conducted'.²¹

- 27 An implication of these arguments is that a single trial design might be judged ethical if applied in one country but not if applied in another. There have been concerns that ethical standards might be imposed on local committees by the sponsoring country. 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? The potential for this kind of disagreement and its resolution is not explicitly discussed in the Guidelines. The Guidelines have an explanatory and expansive role in relation to the Declaration of Helsinki and it is unfortunate that the 1996 revision of the latter document does not appear to acknowledge this.

Implementation of guidelines in developing countries

- 28 Guidelines can only be effective if they are appropriately implemented. In some developing countries individuals may be highly motivated but lack the training or expertise to deal with the problems that arise in applying any set of guidelines. Although this is also a problem in developed countries, it is more severe in some parts of the developing world where resources are often severely limited and where there may be little or no provision for establishing or maintaining a system for the ethical review of research protocols. Longer-term progress will only be made by ensuring that the ethical review process can be properly established, maintained and 'owned' by developing countries. To achieve this, funding to establish and operate ethics committees is needed. However, before research ethics can be taken seriously, there must be 'ownership' of the general principles of medical ethics amongst the medical and research community. More widespread training and discourse amongst researchers and healthcare providers is required.
- 29 Where ethics committees are established in developing countries, they may undertake activities which cast doubt on their independence. For example, although fees may be levied on research projects that are reviewed, payment may be only forthcoming if the local research ethics committee approves the work. How can these committees receive appropriate fees for their work without their independence being compromised? External sponsors may provide a substantial research budget, making it difficult for the

external sponsoring country or international organization'. The host country ethical committees have special responsibility for determining 'whether the goals of the research are responsive to the health needs and priorities of the host country ... assuring the equitable selection of subjects and the acceptability of plans to obtain informed consent, to respect privacy, to maintain confidentiality, and to offer benefits that will not be considered excessive inducements to consent'.

- 21 CIOMS in collaboration with WHO (1993) Guideline 15: p 44. Similar issues have been raised in the UK by the recent introduction of a two-tier ethical review of large-scale trials. Protocols are first submitted to a multi-centre research ethics committee (MREC) and, if approved, referred to relevant local research ethics committees (LRECs) for consideration of 'issues affecting local acceptability'.

ethics committees of less well-off research institutions to make their decisions without consideration of the financial consequences.

- 30 A problem frequently arises with the membership of research ethics committees in developing countries. Members of the community in which the trial is to be conducted may not be represented or may not need to be present for a quorum for the committee to reach a decision. In addition, some members may feel intimidated or may lack the skills to participate in the review process effectively. Inevitably, in many developing countries there may be a limited pool of suitably experienced individuals available to participate in an ethics committee. This may mean that some individuals review proposals in which they may have a material interest.
- 31 In many developing countries, ethics committees may be physically, socially, economically or culturally removed from the population or community which is to be studied. There may be economic and social inequalities which make it difficult for members who are relatively affluent or have high social standing to be able to articulate the views of the poorest members of society. Such tensions are, of course, not unique to developing countries. A local research ethics committee should be constituted so that it understands the local community's customs and traditions. Representation from members of the community who are also able to serve as intermediaries between investigators and participants is needed to determine the appropriateness of any material benefits and ensure that any 'inducements' would be considered in line with the community's gift-exchange tradition. It can be very difficult for a research ethics committee in the sponsoring country to appreciate these subtle issues fully.
- 32 Even where there is recognition of the need and value of the ethical review process and there are suitably trained and experienced persons to participate, lack of finance may be a major constraint. Where ethical review is given a low weighting relative to other pressing budgetary issues, the efficient and effective implementation of any guidelines may not be possible. In the case of multicentre research, the ethical review in each participating centre may not be of comparative quality and the entire process may be extremely cumbersome. There are significant and major delays with any multicentre review process and in this setting the most inefficient committee is likely to be the one with the least experience, capacity and resources. Such a committee may then be effectively excluded from the review process and only 'rubber stamp' external decision making.
- 33 One of the main responses of sponsoring agents and donors from developed countries to these difficulties in achieving local ethical review has been to draw up additional guidelines and to try and ensure that studies with developing country partners are adequately reviewed. Despite such efforts, great difficulties remain with effective and efficient implementation of the Guidelines in some developing countries. This situation is unlikely to improve without raised awareness and an increase in open discussion. The development of increased capacity in scientific research partnerships may need to expand to support expertise and experience in ethical review.
- 34 There is tension between the requirement for research to develop interventions of potential benefit to the host country and the need to make such interventions 'reasonably available' (see paragraph 23).²² Again, this problem is not one that is restricted to developing countries, as research sponsors in developed countries do not

22 CIOMS in collaboration with WHO (1993) Guideline 8: p 25.

The ethics of clinical research in developing countries

guarantee that any resulting product will be available as a condition of undertaking a trial. Even those countries which spend a higher proportion of their national income on healthcare than the UK face ethical dilemmas concerning the distribution of these resources.²³ How should the underlying principles embodied in the Guidelines be interpreted in the light of what can realistically be achieved?

The 'best available' treatment

- 35 The majority of healthcare workers involved in developing country research hope to develop therapies that are relevant and affordable for the local situation and which improve prognoses. The current option may be no treatment, since many developing countries have less than US\$10 per head per year to spend on healthcare.²⁴ The danger is that if an inexpensive intervention is tested against the 'best available' treatment from a developed country then it may be clearly inferior, although it may be substantially better than the locally available option.
- 36 In sub-Saharan Africa approximately 15 million people have been infected by HIV and are likely to die prematurely of AIDS or an HIV-related illness. Even where anti-HIV drugs are available, they are often unaffordable or cannot be delivered by the best route at the required efficiency.²⁵ In many developing countries there is no prospect at present or for the foreseeable future of either widespread anti-HIV drug treatment or monitoring of side-effects in many of those who might be treated. A strong case can therefore be made for studies which compare alternative interventions with the current standard local therapy, even if that standard is no treatment. Such studies address the question of whether a novel affordable intervention has some benefits as compared to current standard treatment. They do not, and are not intended to, address the question of whether the intervention is as good as other currently unaffordable treatments.

Non-therapeutic research

- 37 There has been criticism of the distinction made between the terms 'therapeutic' and 'non-therapeutic' research, and in some countries, such as the US, the terms have largely been abandoned.²⁶ This is because of a growing recognition that most therapeutic clinical trials contain non-therapeutic components. The use of the term 'non-therapeutic research' is often restricted to clinical studies on healthy volunteers or even patients, where the study is not intended to directly benefit the individual, for example, short-term Phase I or II trials to establish dosage and safety of a new drug. Its use has also been extended to cover epidemiological and pathological studies. Non-therapeutic research into the epidemiology and pathogenesis of clinically important diseases in a local context continues to be needed in developing countries. As in the case of therapeutic research, non-therapeutic research should be approved by a local research ethics committee.

23 Weale A (ed) (1988) **Cost and Choice in Healthcare**, p. 11, King Edward's Hospital Fund for London, London.

24 Bobadilla JL, Cowley P, Musgrove P and Saxenian H (1994) Design, content and financing of an essential national package of health services, **Bulletin of the World Health Organization**, 72: 653–662.

25 Clark M, Collinson A, Faal H, Gaye A, Jallow M, Joof-Cole A *et al.* (1998) Ethical issues facing medical research in developing countries, **The Lancet**, 351: 286–287.

26 Here we use the term 'therapeutic research' to indicate research having the potential to produce a real and direct benefit for the participant and 'non-therapeutic research' to mean research without such potential.

- 38 Are there special ethical considerations which should be taken into account when designing non-therapeutic studies? These may include steps to promote respect for participants by placing particular emphasis on the genuineness of consent, including an assessment of the consent procedure and the appropriateness of any inducements to participate. It can be more difficult to explain the rationale and potential benefits of non-therapeutic research than to explain the benefits of a comparison of two drugs in a therapeutic study. Paradoxically, it may be easier to bring openness to the informed consent process, as there is less chance that the individuals will believe that they might benefit directly from participating in the research study.
- 39 Epidemiological studies which only involve examination of medical records may be conducted in some circumstances without the consent of the individuals concerned, providing that confidentiality is assured. Some guidance suggests that archived samples of blood, other body fluids or tissue specimens, may be tested without consent using unlinked anonymous methodology.²⁷ However, the CIOMS Guidelines state that consent should 'usually be sought' from such individuals, a proposal which has been criticised as impractical.

Consent to participate in clinical research

- 40 A request for consent to participate in research is an expression of respect for human dignity and autonomy. It has been argued that there is a greater responsibility to protect the interests of participants when research is conducted by researchers from developed countries in developing countries. Researchers should use their best endeavours to ensure that participants understand the proposed research and its implications. This is particularly important in areas where the level of education of potential participants is low. In both developed and developing countries, the ability to disclose appropriate information to enable those involved in any research to give genuine consent may be limited by the need to translate such information into local dialects. Particular terms, such as placebo, for which there may be no locally equivalent concept, can be especially difficult to define. If the research requires randomisation, it is necessary to explain this process to patients, together with the concept of equipoise.²⁸ In societies where there is absolute trust in the abilities of the physician, an admission of such uncertainty may undermine trust and confidence, or consent may be given on trust by participants without an understanding of the research.
- 41 Researchers have adopted a number of measures to ensure that the information they provide is of an appropriate quality to allow prospective participants to give genuine consent to participate in research. These measures include carrying out an iterative process of translation and back-translation until an accurate translation is achieved and identifying local perceptions of disease and treatment in ongoing discussions with the populations from which research participants are being drawn. For such measures to be carried out translators need to be recognised as critical members of the research

27 World Health Organisation Global Programme on AIDS (1989) **Unlinked Anonymous Screening for the Public Health Surveillance of HIV Infection. Proposed International Guidelines**, WHO, Geneva.

28 Equipoise 'a term used in relation to clinical trials and in justification of randomisation ... denotes the state of mind of clinicians, individually or collectively, who have no rational preference among the treatment options to be compared ... An important aspect is whether the patients or subjects concerned share the clinicians' equipoise regarding the possible burdens (including side-effects) as well as potential benefits of the treatments being compared' (Boyd KM, Higgs R and Pinching AJ (eds) (1997) **The New Dictionary of Medical Ethics**, BMJ Publishing Group, London).

The ethics of clinical research in developing countries

team and recruited, trained and regarded as such. Translators will also need to respect the confidentiality of participants' medical information.

- 42 Providing sufficient and appropriate information to participants to enable them to genuinely consent to participate in research requires some form of dialogue: a participant's signature on a consent form does not, of itself, demonstrate informed consent. What measures should researchers adopt to respect the variety of ways in which different communities wish to receive information and reach decisions about matters such as participating in research? In the majority of circumstances, consent may be given after the provision of appropriate written material and following discussions with researchers. Particular concerns occur when prospective participants receive all their information about a trial verbally, either because they are illiterate or speak a dialect with no written form. In such situations there is a danger that the information conveyed to participants may be inaccurate, in part because translators may feel more successful if they persuade participants to enrol, and may consequently gloss over risks and side-effects in order to achieve a high acceptance rate. Consent given on the basis of such incomplete or misleading information cannot be genuine.
- 43 For consent to be genuine, it must be freely given. There are many factors which may affect the ability of prospective participants in the developed and developing world to consent freely to or refuse to participate in research. These include situations where benefits, such as payments, accruing from participating in research, amount to undue inducements and pressures from other parties are such that participants feel that they have no choice but to give consent.
- 44 The dividing line between inducement and benefit is a fine one. At what point does the provision of medical services or reimbursement for a participant's time amount to an undue influence on a participant's decision to take part in the research? Inducements which have been considered acceptable during research include money in the form of payments for travel, inconvenience or work lost, food, photographs or film, health care for individuals or their families during the trial, and non-therapeutic community health interventions. Decisions about which particular inducements are ethically acceptable will depend on local circumstances and only those with local knowledge can make appropriate distinctions.
- 45 In many developing countries there is a drastic shortage of medical staff and supplies. In order to improve patient follow-up in clinical research, the research team will often maintain walk-in clinics where patients may attend without appointments and with minimal waiting times. Participants may also be offered free medical care within the context of the study clinic and this may act as an incentive for them to attend the clinic regularly. How should the need for mechanisms to ensure adequate follow-up of participants be balanced with the need to avoid undue inducements?
- 46 Reimbursement of expenses and free medication may also be offered to participants during research and may influence them to consent to, or remain in, a study. This practice is often necessary in developing countries where high unemployment means that participants are only able to take part in research programmes with such support. Failure to reimburse participants for their time may also be considered insulting. If reimbursement of participants' costs and time only covers the true costs involved then this approach may not act as an undue influence. However, it should not be overlooked that even the poorest and least powerful may have altruistic motives for participating in research: altruism is not a consequence of 'development'.

- 47 An additional factor that may influence a patient's decision to consent to participate in a study is their respect for the medical staff. Consent to a study may be given simply because a doctor has asked for it. It may be difficult for doctors, aware of the attitudes of their patients, not to use this to influence a patient's decision to take part in a study and care must be taken to ensure that any consent is genuine. Under these circumstances, the role of other healthcare workers, such as nurses, in the consent process may be important as prospective participants may then find refusal to participate easier. This problem is not restricted to developing countries although it is likely to be more pronounced in them.
- 48 In many developing countries the concept of individual autonomy may be absent from the social structures of some societies. An individual is seen as an integral part of a family or community and therefore has to consult elders, parents, spouses or even children, before consenting to any medical or surgical procedures. In some areas it is seen as necessary to obtain the consent of community leaders before any research is carried out. Researchers should be aware of the tension which may arise in communities simply as a result of asking for such consent.²⁹ In some cases, women may have to obtain the consent of their husbands to participate in research. Should researchers endeavour to obtain the consent of the woman herself? If the family has reservations about participating in the research, should these be honoured regardless of the woman's stance? Is research acceptable in situations where community elders or family members consent on behalf of participants who, in the developed world, would be considered capable of consenting for themselves?³⁰
- 49 In both the developed and developing worlds there is much discussion of the extent to which research is justified on those who do not have the capacity to consent, such as small children and the unconscious. The question of what research is permissible on children is particularly pertinent to this discussion paper because in parts of the developing world a large burden of ill health falls on children and consequently a very substantial part of local clinical and epidemiological research involves them. In many developed countries children may be considered to have the capacity to consent to research or, where they do not, their parents or guardians may be able to give proxy consent. It is also often considered acceptable to conduct research on children only when the equivalent information cannot be obtained from research on adults or older children who have the capacity to consent. In many developing countries there is a different view of childrens' moral status in relation to their parents, other family members and the community as a whole than that which prevails in some developed countries. What steps should researchers and research ethics committees take where local perceptions of the status of children result in decisions such as consent being given on behalf of a child who has the capacity to consent for themselves?

29 For example, one research team found that a family was expelled from their village for refusing to take part in research that their village elder had consented to.

30 The question of who gives consent to the inclusion of a country in clinical trials where entire villages or communities, rather than individuals, would be randomly allocated to the control or intervention arm of a trial, is a difficult one.

Ethical issues raised by HIV/AIDS vaccine trials

- 50 One of the ethical issues raised by developed countries' undertaking or sponsoring clinical research in developing countries is the type and level of care and treatment to be made available to clinical trial participants who become infected with HIV in the course of a trial or who are found to be infected when screened for entry to a trial. One view is that the treatment provided should be that which is routinely offered to HIV-infected individuals in developed countries. Others have argued that it is ethically acceptable to provide treatments based on what is routinely available in the host country.
- 51 A question arising from the controversy surrounding the conduct of studies of perinatal transmission of HIV using placebos controls in Thailand and Africa is whether, in future, such disputes might be identified and addressed in advance of initiating the research. The Joint United Nations Programme on HIV/AIDS (UNAIDS) vaccine development programme sought to anticipate the dilemma by adopting a procedural solution to this and other ethical concerns likely to arise once vaccine efficacy trials commence. A series of regional conferences culminated in the preparation of a Guidance Document on Ethical Considerations in International Trials of HIV Preventive Vaccines. In its current, provisional version, the Guidance Document calls for a move away from the paternalism of the recent past to a recognition of the entitlement of all countries to be self-determining. In particular, it calls for the process of planning and conduct of international clinical trials in the field of HIV vaccine development to involve joint ventures between collaborating partners who share equally in decision making and in responsibility for carrying out the trials.
- 52 What type of care and treatment should be available to vaccine trial participants? There is wide agreement about the need for provision of counselling for all trial participants about ways to minimise the risk of becoming infected with HIV/AIDS. Research participants must not only be informed about the details of the research itself, but they must also receive high quality counselling from personnel who are independent of the research team.
- 53 The main ethical problem related to the design of HIV vaccine trials stems from the need to measure different endpoints. The primary objective of an efficacy trial may be to determine whether the vaccine prevents infection in individuals exposed to the virus. Many leading vaccine researchers believe that a vaccine is unlikely to have that effect, but it may keep the viral load low following infection, thereby preventing progression to disease. Herein lies the problem: because triple therapy as currently provided on a routine basis in the US effectively lowers the viral load and interferes with the ability to measure the efficacy of an HIV vaccine in preventing disease. The real problem is therefore whether or not to treat participants who become infected during the course of the study.
- 54 How can this dilemma be addressed? One approach might be to distinguish between measures which are, strictly speaking, part of the research design and measures which are part of routine clinical care. Accordingly, the provision of anti-retroviral treatment for individuals who become HIV-infected would be a matter of clinical care, not an integral part of the research design of vaccine trials. While the research design must adhere to international ethical standards of research, the provision of clinical care to HIV-positive individuals who seroconvert during the trial may be a function of what is practically available in each country. Although some people might be persuaded by this line of

reasoning, it is unlikely to convince others who maintain that any attempt to distinguish between conducting research and providing treatment is artificially drawn in order to circumvent the ethical principle, which is that a duty of care is always owed to trial participants.

After the trial is over

- 55 The clinical problem that a particular study was designed to address will, in most cases, remain when the trial has been completed. The nature of the ethical issues raised once a trial is over will be determined partly by the type of study and the disease and partly by the social and economic features of the site where the trial was conducted. However, there are ethical issues which arise in nearly all cases. These can be divided into two categories: those that apply to all trials and those that are dependent upon the trial's outcome.

Issues arising in all trials

- 56 The results of a clinical study, particularly if a therapy proves to be successful, are likely to be broadcast widely in the scientific press and to be presented to the medical authorities in the area where the trial was done. However, it is equally important that results of the trial should be fed back in a comprehensible manner to the trial participants as well as the field staff who were responsible for the collection of routine data. Participants are often very supportive of the efforts of the investigators, even when the outcome has been disappointing. Failure of investigators to have presented results of a previous trial is a frequent reason for subsequent non-participation in a research study.
- 57 Participants in a clinical trial in a developing country with a poorly financed health service usually benefit from participation in the trial, even if they are in the control group. In clinical trials, the need for repeated clinical observations may necessitate regular visits to see an experienced physician. These would be financed by the trial and might benefit the participant's health overall. Where such trials are on a large scale, this benefit may extend to the whole community, including those not involved directly in the trial. For example, it may be necessary to improve referral systems and diagnostic facilities at peripheral centres. Routine immunisation programmes may need to be strengthened before vaccine trials can be conducted. How can these benefits be integrated into existing healthcare? We have already noted that the benefits tend not to be sustained once the trial is completed. To what extent healthcare benefits should be sustained after the trial is over and by whom are difficult problems for researchers, sponsors and pharmaceutical companies to resolve.

Issues dependent on trial outcome

- 58 We have seen that in some cases prevention of infection in infancy or early childhood may have the effect of postponing serious adverse outcomes until the child is older.³¹ The situation in vaccine trials is more difficult. Because most vaccines induce an immunity that declines with time, there are strong scientific grounds, where a vaccine has been shown to be effective, for maintaining the control group so that the duration

31 See paragraphs 4-5 for examples of *Haemophilus influenzae* type b (Hib) infections and preventive treatment in malaria.

of vaccine-induced protection can be determined. However, this may be considered unethical and it may be proposed that control participants should be offered vaccination with the effective new vaccine on completion of the trial if they remain at significant risk, despite the fact that finding the control participants to administer a 'catch-up' vaccine may be difficult and costly. Is it ever ethically acceptable for a study to begin without a decision having been made as to whether or not control participants will be offered vaccination on completion of a trial (depending on the trial results)? Can participants be said to have given a genuine consent if they have not been informed of such a decision before enrolling in a trial?

- 59 Is there an ethical responsibility to ensure that an effective therapy or procedure is provided after the trial is over and on whom does such a responsibility fall? We have noted above that this issue will become increasingly important during the next few years as more vaccines are tested in developing countries (see paragraph 17). Should other individuals or groups in the country thought to be at high risk for infection receive a vaccine? Should all with a perceived need in the country receive a vaccine, and if so, for how long? Should a vaccine be supplied to other countries with a high incidence and prevalence of the disease in question? What is the degree of efficacy a vaccine must demonstrate in order to warrant wide distribution and who should provide it? There will be a need for pragmatism as each case will be different. The responsibility for implementing a vaccine or therapy will generally not lie with any one group. If a national government has agreed to a trial, it presumably accepts some responsibility but there will need to be negotiations and partnership between the various interested parties. There is general agreement that the investigators have some responsibility but disagreement about how far that responsibility goes. Links between the public and private sector in developing countries may improve the opportunity for some therapies to be made available at low cost. However, there is a danger that research may be limited if the implications are too great for policy makers or non-profit and commercial funding bodies. These vexing questions call for a solution that meets the ethical requirement of distributive justice, yet they remain among the most difficult to answer from an economic and practical standpoint.
- 60 The report of the successful outcome of a trial raises ethical issues for those undertaking similar trials in other communities. Must they stop their trial? Should the researchers offer the new proven treatment to all their research participants? Should a trial steering committee, advised by a data and safety monitoring committee, take this decision because it would be inappropriate to put such a responsibility on the investigators who have invested so much in a study? If trial populations are very different, for example one in a developing and the other in a developed country, then it may be ethically justifiable to allow the second trial to continue as it may be in the population's best interests. A general problem with the validity of research results arises when comparisons have to be made between trials with different end-points. For example, if a relatively small trial shows that a new vaccine has a dramatic impact on the incidence of pneumonia, is it legitimate to continue in a similar community with a larger trial of the same vaccine which is designed to measure the effect on mortality resulting from pneumonia?
- 61 A circumstance which may cause particular problems for the investigators is the demonstration that those in the active treatment or prevention group are *worse off* than those who receive conventional management or a placebo. If the effect is marked, it should be detected by the data safety and monitoring committee during the course of the study and the trial halted earlier than planned. In the case of treatment trials in which an adverse outcome is recorded in the group who received the new drug, it is

usually relatively straightforward to restart treatment with conventional therapy in these patients. However, the situation may be much more difficult in the case of vaccine trials because the experimental vaccine may have put the trial participants at enhanced risk not only during the period of the trial but also for a further period. When faced with unexpected results, it has been argued that investigators and their sponsors are under a strong ethical obligation to do everything possible to mitigate any potential harm to trial participants. This raises the question of compensation for persons injured during the course of research. It is unclear who has responsibility for meeting any medical expenses. UK public sector research funding bodies such as the MRC may not offer advance indemnities nor take out commercial insurance for non-negligent harm. The MRC only offers the assurance that it will give sympathetic consideration to claims in respect of non-negligent harm arising from a MRC-funded trial.

- 62 A successful clinical trial is likely to raise a number of ethical issues for the health authorities of a developing country which should be discussed before a study begins. Some of these may be only relevant locally but others are of a more general nature that will apply in other similar situations. As more experience is gained in managing some of these difficult issues, it is important that ways are found of making this experience generally accessible so that each group of investigators does not have to tackle from the beginning the many problems likely to arise when a large trial is over.
- 63 Over the past five years, the pharmaceutical industry has shown increased interest in developing medication specifically for diseases prevalent in developing countries. If, however, there is an expectation that industry should provide expensive drugs free of charge after the research is over, this interest will be short-lived. The question of who is responsible for making new drug treatments 'reasonably available' needs to be addressed. The potential use of typhoid vaccine in Nepal is a useful example which illustrates the failure of the existing guidance to cover all eventualities. Although this vaccine is relatively cheap, it is beyond the means of government to make it available in Nepal. Similarly, in developing countries such as India and Thailand there is an issue about which sectors of society will benefit from trials to manage the vertical transmission of AIDS. As we have noted, the Guidelines do not provide adequate guidance on the issue of 'reasonably available'.
- 64 Some argue, however, that the Guidelines should not be so rigid that they do not allow for exceptional situations. A similar donation programme to that described for Ivermectin (paragraph 7) has been developed for Albendazole, which is used in the treatment of lymphatic filariasis, an infection caused by parasitic worms which often leads to elephantiasis (an enlargement of the arms, legs and genital organs). Cheaper ways of producing mefloquine, a new malaria drug which is currently too costly for most developing countries, are also being sought. Once treatments are shown to be effective, discussion has enabled adequate supplies to be secured in some cases. However, the problem of whether a product will be made available after a successful trial is one that occurs in all countries, rich and poor. The idea that a trial should not be undertaken unless there is a guarantee that the product will be widely available at low cost after the trial is generally untenable and may limit development of effective therapies. Such decisions are largely determined by government and not investigators. While researchers cannot insist that a supplier provides drugs after the research is over, they can nevertheless demand that these issues are discussed openly at the outset of research protocol development. One compromise that is sometimes adopted is that drugs are provided for participants in the trial (if effective) but not necessarily for the community at large.

The need for future work

- 65 The sponsorship of clinical research in developing countries by developed countries raises important ethical issues. However, the majority of these issues are neither new nor confined to such research. The ethical requirements of respect for human participants and human dignity and the limitation of harm to patients are already well established in clinical research and embodied in international guidelines and declarations. Nevertheless, developing countries may have differing conceptions of such principles, such as how consent should be obtained to participate in a research protocol in a manner which respects the participant and community. Questions of justice are also particularly relevant where limited resources mean successful therapies and vaccines may be unaffordable.
- 66 International statements concerning the ethics of biomedical research such as the Declaration of Helsinki and CIOMS Guidelines are therefore important and necessary. Yet they pose a number of questions when clinical research in developing countries is being considered. Should the Guidelines and the Declaration 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 clinical research in developing countries that need to be addressed? In particular, how should areas of ambiguity, such as those concerning applicable standards of care, be resolved? Are there conditions under which it is impractical or inappropriate to follow the Guidelines in their current form? How can the Guidelines and Declaration be better disseminated amongst those who are currently unaware of them?
- 67 The Guidelines and the Declaration cannot be effective unless accompanied by the training and resources required for their effective implementation in developing countries. 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. Are research committees the best means of protecting the interests of developing communities? What is the most effective way to involve local investigators, other health professionals, pharmaceutical companies and government agencies in the development of research protocols so that such research can offer most benefit to the community? Such consultations may highlight specific issues about receiving genuine consent from groups such as women and children to participate in research. How can such concerns about the conditions under which consent is secured be resolved?
- 68 There is clearly a very considerable distance between the broadly based principles outlined in international guidance and the practical issues being considered by local research ethics committees reviewing individual protocols. Is the most appropriate way forward to produce 'intermediate' guidelines to link these two levels of ethical assessment and if so, should they be generated by national or international bodies? Concerns that the controversy associated with HIV/AIDS perinatal transmission trials has directed attention away from the wider issues discussed in this paper may prove to be unfounded. The recent debate has stimulated a number of bodies including the Nuffield Council on Bioethics, the World Health Organization, the US National Bioethics Advisory Commission and the US National Institutes of Health to consider some of the issues arising from sponsorship of developing country clinical research by developed countries. The importance of bringing these initiatives together to form coherent guidance has already been acknowledged by many of the bodies concerned.

Appendix

Criticism of the zidovudine trials to prevent perinatal HIV transmission

In September 1997, a paper published by Lurie and Wolfe¹ and an editorial by Angell² in the *New England Journal of Medicine*, and an editorial in *The Lancet*³ criticised placebo-controlled trials of short-course zidovudine given to HIV-infected pregnant women to prevent perinatal HIV transmission. The trials, some of which were conducted under the aegis of UNAIDS and WHO, were designed to determine whether relatively affordable courses of zidovudine given to pregnant women would reduce the risk of mother-to-child transmission in the way that longer, more expensive and complex courses were shown to do in a trial (076) conducted in the US and France.⁴ The placebo-controlled trials were conducted in countries where conventional local pregnancy care excluded zidovudine and had been approved by local ethics committees in the host countries. Such trials would be unethical in developed countries where long-course zidovudine has been the best proven therapeutic method since the completion of the 076 trial.

Lurie and Wolfe's paper, Angell's editorial and *The Lancet* editorial have been criticised as showing a lack of understanding of the realities of health care in developing countries.⁵ Lurie and Wolfe, and Angell argued that no patient participating in a trial supported by US funds should be denied the 'standard of care' available in the US, citing the Declaration of Helsinki and the CIOMS Guidelines in support. However the relevant section of the Declaration of Helsinki (Principle II-3), may be interpreted in two ways: either to refer to the best proven diagnostic and therapeutic method internationally, or to indicate the best proven diagnostic and therapeutic method usually available in the country where the trial is being conducted. The former interpretation does not acknowledge the self-declared role of the CIOMS Guidelines, which is to explain 'how the Declaration of Helsinki could be effectively applied, particularly in developing countries given their socio-economic circumstances, laws, regulations and executive and administrative arrangements'. Such an interpretation of Principle II-3 would exclude almost any locally relevant controlled trials where the control group received no treatment (with or without placebo) or a comparison treatment which was less than the optimal treatment available in a developed country. However, the CIOMS Guidelines state that research in developing countries should be 'responsive to the health needs and the priorities of the community in which it is to be carried out'.⁶ If such locally responsive research could not be conducted this would lead to Ministries of Health in developing countries being deprived of the information needed to plan their allocation of their

-
- 1 Lurie P, Wolfe S M (1997) Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries, **New England Journal of Medicine**, 337: 853–856.
 - 2 Angell M (1997) The ethics of clinical research in the third world, **New England Journal of Medicine**, 337: 847–49.
 - 3 Editorial (1997) The ethics industry, **The Lancet**, 350: 897.
 - 4 Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ *et al.* (1994) Reduction of maternal-infant transmission of human immunodeficiency virus type-1 with zidovudine treatment, **New England Journal of Medicine**, 331: 1173–1180.
 - 5 Aaby P, Babiker A, Darbyshire J, Nunn A, Barreto S, Alonso P *et al.* (1997) Ethics of HIV trials, **The Lancet**, 350: 1546; Halsey N A, Sommer A, Hendreson D A and Black R A (1997) Ethics and international research, **British Medical Journal**, 315: 965–966.
 - 6 CIOMS in collaboration with WHO (1993) **International Ethical Guidelines for Biomedical Research Involving Human Subjects**, Guideline 8: 25, CIOMS, Geneva.

The ethics of clinical research in developing countries

limited resources using an evidence-based approach.⁷ Nicoll has suggested that these arguments could render the initial trial of Hepatitis B immunisation in West Africa,⁸ the Mwanza trial of STD intervention against HIV and many other community trials invalid.

A second aspect to the arguments in the articles by Lurie and Wolfe, and Angell, was whether or not a single international ethical code existed. Angell argued that there was such a code, citing the Declaration of Helsinki and the CIOMS Guidelines, and proposed that any trial sponsored from abroad should be judged ethical in both host and source countries. The Guidelines would seem to support this as they state that 'the ethical standards applied should be no less exacting than they would be in a case of research carried out in that [the source] country'. However, the Guidelines go on to provide flexibility, indicating that the host country ethics committee has special responsibility for matters of detail in a trial, such as determining the acceptability of plans to obtain informed consent. In contrast, committees in the sponsoring country need only to be satisfied that the trial conforms to broad ethical standards. If Principle II-3 referring to the 'best proven diagnostic and therapeutic method' is interpreted as meaning the best locally available proven diagnostic and therapeutic method, it would allow the flexibility required for developing countries research to 'be responsive to the health needs and priorities of the community in which it is to be carried out'.

7 Nicoll A (1999) Are existing guidelines good enough? **Nuffield Council on Bioethics Workshop on the Ethical Issues of Clinical Research in Developing Countries**, 21–23 February 1999, London.

8 Hall AJ, Inskip HM, Loik F, Day NE, O'Connor G, Bosch X *et al.* (1987) The Gambia hepatitis intervention study, **Cancer Research**, 47: 5782–5787.

Glossary of acronyms

AIDS Acquired immunodeficiency syndrome

AZT azidothymidine (more recently called zidovudine)

CIOMS Council for International Organizations of Medical Sciences

HIV Human immunodeficiency virus

STD Sexually transmitted disease

UNAIDS United Nations Programme on HIV/AIDS

WHO World Health Organization

Glossary

AIDS and HIV. AIDS represents a range of diseases associated with HIV, a viral infection producing a slowly progressive weakening in the cellular immune system, mainly characterised by substantial reductions in CD4+ lymphocytes. HIV infection is transmitted via sexual intercourse, by blood–blood contact, by the birth processes and by breastfeeding. AIDS develops via direct HIV effects such as neurological changes and secondary effects such as infections and tumours due to an inadequate immune response.

Antiviral interventions. Drugs which act against viral infections.

Control. A control group contains participants who remain untreated or who are treated with drugs/methods currently used in clinical practice. The results from this group are compared with those of another group of individuals who are given the novel treatment which is being tested.

Epidemiological. Concerned with describing and explaining the occurrence of disease in populations.

Equipoise. A state of being equally balanced, said of moral, political or social interests or forces.

Hepatitis. Infection of the liver which can be caused by specific viruses.

Hepatitis B. A virus transmitted through all body fluids by poor surgical sterilisation procedures, close contact, blood contamination, infection at birth, needle sharing or sexual contact. It causes an acute illness, which may resolve into or cause chronic hepatitis.

Infectious diseases. Diseases caused by living organisms, primarily viruses, bacteria and fungi. Diseases can be transmitted by airborne spread, physical contact, inoculation (by needle or insect) or by food and drink. Organisms then enter the body, resulting in infection, either by inhalation or direct contact.

Intrapartum. Within/during childbirth.

The ethics of clinical research in developing countries

Longitudinal studies. Studies in which the same individuals or group of individuals are examined on a number of occasions over a period of time.

Non-therapeutic research. Research which has no curative basis but may facilitate understanding of disease processes or the early phase of drug development.

Pathogenesis. The mode of production or development of a disease.

Phase I trials. The treatment is tested in a few, often healthy, people to learn whether it is safe and what happens when the drug enters the body.

Phase II trials. The treatment of a larger number of patients is tested to see if it is active and safe in the short term and to determine the dose.

Phase III trials. The efficacy and safety of the treatment on several hundred to several thousand patients is assessed, often at many different clinics or hospitals. These trials usually compare the new treatment with the standard treatment already in use or, sometimes, with no treatment.

Phase IV trials. After a drug has been approved, these trials assess its safety and wider role in therapy.

Placebo. A treatment known to be without effect, usually used as a control to be compared against a potentially effective substance or method which is being subjected to clinical trial.

Postpartum. Following childbirth.

Retroviruses. RNA viruses in which during viral replication, the RNA is copied into DNA by the enzyme reverse transcriptase. The resultant DNA then integrates with the host chromosomal DNA. HIV is a retrovirus.

Seroconversion. The production of antibodies in response to infection. These are detectable via blood testing and pinpoint infection indicative of a specific disease, such as HIV.

Therapeutic. Aiming to cure an identifiable disease or condition.

Triple drug combination. Combination of three drugs, for example nevirapine, didanosine and zidovudine, used in the treatment of those infected with HIV.

Typhoid. Serious infectious disease characterised by fever, severe general illness usually characterised by delirium or stupor and organ enlargement or pain. Infection is from person to person, transmitted by the urine or stools of patients or symptomless carriers.

Zidovudine. An antiviral drug now used mainly in developed countries in the triple drug combination for the treatment of HIV/AIDS.

Nuffield Council on Bioethics
Publications List

To: **Ms Yvonne Melia**
Nuffield Council on Bioethics
28 Bedford Square
London WC1B 3EG UK
Fax: +44 171 637 1712 Telephone: +44 171 681 9625
Email: bioethics@nuffieldfoundation.org

From: _____

Please send me _____ copy(ies) of _____ £
Genetic screening: ethical issues @ £7.50 each
Reprinted October 1997

Please send me _____ copy(ies) of _____ £
Human tissue: ethical and legal issues @ £10.00 each
Published April 1995

Please send me _____ copy(ies) of _____ £
**Animal-to-human transplants:
the ethics of xenotransplantation @ £10.00 each**
Published March 1996

Please send me _____ copy(ies) of _____ £
Mental disorders and genetics: the ethical context @ £20.00
Published September 1998

Please send me _____ copy(ies) of _____ £
Genetic modification of crops: the ethical and social issues @ £20.00
Published May 1999

**Prices include cost of postage *within* Europe, please add
£3.50 per copy for postage *outside* Europe**

TOTAL £

I enclose a cheque for £_____ made payable (**in sterling**) to the **Nuffield Foundation**, or
Please debit my credit card £_____

Visa/Mastercard/Eurocard no: (**not American Express**) Expiry date:
_____/_____/_____/_____/_____ ____/____

Name on card _____
Address of cardholder _____

Postcode _____

Authorised signature _____