



The ethics of research related to healthcare in developing countries

a follow-up Discussion Paper

NUFFIELD
COUNCIL ON
BIOETHICS

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The ethics of research related to healthcare in developing countries

**a follow-up Discussion Paper based on
the Workshop held in Cape Town, South
Africa 12–14th February 2004**

**NUFFIELD
COUNCIL ON
BIOETHICS**



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- 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

There is a bewildering multiplicity of guidelines, regulations, declarations and recommendations on the ethics of research relating to healthcare in developing countries. They tend to be both too general to provide answers to practical problems that arise in the course of research, and too specific in that they fail to take account of differing circumstances in developing countries.

The Nuffield Council on Bioethics co-hosted a very productive Workshop with the Medical Research Council of South Africa in Cape Town in February 2004. The Workshop was a follow-up of the Council's Report on *The ethics of research related to healthcare in developing countries*, published in 2002. The Council was delighted to provide an opportunity for researchers, sponsors and members of ethics committees from developed and developing countries to discuss the themes of our Report, and to consider how the various guidelines are applied in practice. Fifty-eight participants from 28 countries pooled their considerable expertise to discuss and debate the issues. We were able to sponsor delegates to attend the Workshop, with the assistance of the UK Department for International Development, the UK Medical Research Council, the Wellcome Trust and the Rockefeller Foundation. We are grateful to them for their generous support.

It was fitting that this meeting was held on the African continent and was co-hosted with the Medical Research Council of South Africa (MRC), which has been at the forefront of developing ethical standards in clinical research. We are most grateful to colleagues from the MRC for their valuable assistance in organising the Workshop, particularly Mandy Salomo and Deidre Raubenheimer. The Council is, as usual, much indebted to its own staff from the Secretariat for their unstinting efforts to ensure that the Workshop was a success. Particular thanks are due to Nicola Perrin (Public Liaison Manager) for her excellent contribution.



SIR BOB HEPPLER QC FBA
Chairman

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Dr Jerry Coovadia, Dr Liza Dawson, Professor Brian Greenwood, Professor Adetokunbo Lucas and Mr Peteris Zilgalvis peer reviewed an earlier version of this Paper and Dr John Williams commented on Chapter 6. Ms Shawneequa Callier conducted research for the background paper for the Workshop during an internship at the Council in August 2003. Nicola Perrin organised the Workshop and made a substantial contribution to this Paper. The Council is deeply grateful to them all.

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Executive Summary

Many people in the developing world suffer from poor health and reduced life expectancy. The role of research that contributes to the development of appropriate treatments and disease prevention measures is vital. However, lack of resources and weak infrastructure mean that many researchers in developing countries have very limited capacity to conduct their own clinical research. They therefore often undertake research in partnership with groups from developed countries. A sound ethical framework is a crucial safeguard to avoid possible exploitation of research participants in these circumstances.

Much attention has been given to providing guidance which addresses ethical issues raised by externally sponsored healthcare-related research in developing countries. A number of international organisations have recently revised existing guidelines or prepared new ones (see paragraphs 1.9–1.15 and Appendix A). The Council held a Workshop, co-hosted with the Medical Research Council (MRC) of South Africa, in February 2004 to explore the practical implications of new and recently revised guidelines since the publication of the Council's 2002 Report.¹ This Paper reports the discussions of four topics at the Workshop: consent, standards of care, what happens after the research is over, and ethical review.

Delegates emphasised that applying guidance in practice is often fraught with difficulty. When the different guidelines are compared, they are markedly inconsistent in some areas. The guidelines vary with regard to the scope and level of detail of information to be provided in the consent process (paragraphs 2.9–2.16), the obligation to provide a universal standard of care to control groups (paragraphs 3.6–3.10), the use of placebos (paragraphs 3.11–3.15), and the extent to which research participants are owed access to successful therapeutics after research is complete (paragraphs 4.4–4.17). There is also variation with relation to the degree of involvement of the host country in the review process (paragraphs 5.8–5.15).

Furthermore, some of the guidelines establish standards that are inappropriate for the developing country setting. A number of case studies provided by delegates illustrate difficulties which have arisen. These include obtaining consent in emergency settings (paragraph 2.7), providing the universal standard of care for control groups in vaccine trials (Box 3.2), and securing guarantees from sponsors or physicians that access to successful therapeutics will be provided to participants once a trial is over (paragraph 4.12). Faithful adherence to some of the provisions within the guidelines is often unachievable. Moreover, despite attempts at clarification, the status of pre-eminent guidelines such as the Declaration of Helsinki, is viewed by some as merely aspirational and by others as akin to regulation. The possibility that researchers may forgo conducting valuable research in developing countries because sponsors in developed countries or review committees in sponsor countries may judge it incompatible with specific provisions of guidance continues to be a cause for concern (paragraphs 6.26–6.34).

Researchers, sponsors and members of ethical review committees must judge for themselves how to approach some of these complex issues. In some countries they will be assisted by national guidance that takes account of local needs and the cultural context. Aligning externally sponsored research with national research priorities (paragraphs 6.22–6.25), and initiating early discussion of the issues with national authorities as well as the local communities concerned, will provide researchers with a crucial counterbalance to the generalised and sometimes unsatisfactory framework of international guidance. The existence of independent research ethics committees is crucial in achieving this aim (paragraphs 5.1–5.24).

Continued

¹ Nuffield Council on Bioethics (2002) *The ethics of research related to healthcare in developing countries* (London: NCOB).

The Paper draws together some of the general themes that were discussed during the meeting, including community participation, the development of expertise, sustainability, partnership and ensuring feedback from research (paragraphs 6.2–6.12). Issues requiring further discussion are also identified, including those raised by chronic diseases, research on public health, and intellectual property (paragraphs 6.13–6.21).

Chapter

Introduction

1



Introduction

Background

- 1.1 Research is urgently needed to help to address the burden of disease that affects the developing world. The ability of researchers in poor countries to conduct their own clinical studies is severely impeded by limited funds and a lack of trained staff. Socio-economic factors are also influential. For example, opportunities in education and research, the integrity of family life and the quality of national and local governance all play a part. It is vital therefore that developed countries should help to establish partnerships, involving both the public and the private sector, to conceptualise, design, implement, fund and assess healthcare-related research in developing countries. However, the inequalities that exist between developed and developing countries pose significant risks of exploitation when externally sponsored research is carried out.
- 1.2 Several of the issues raised by externally sponsored research, such as the standard of care provided to research participants, are not confined to developing countries. They tend, however, to be exacerbated in situations where provision of basic healthcare is limited, and where research ethics committees are under-resourced or even absent, as is often the case in developing countries. In addition, researchers are faced with diverse and sometimes conflicting guidance as to what may be ethically appropriate.
- 1.3 International guidelines to protect participants in biomedical research have been in place for several decades. Specific guidelines on the ethics of healthcare-related research have recently been revised by a number of international bodies, including the World Medical Association (WMA), and the Council for International Organizations of Medical Sciences (CIOMS). New guidelines have been prepared by the European Group on Ethics in Science and New Technologies (EGE) and the Council of Europe's Steering Committee on Bioethics (CDBI) (see paragraphs 1.9–1.14 and Table 1.1). The reasoned application of the available guidelines in the light of ethical principles is a primary aim of ethical review of research proposals. However, variation in the guidelines provided by these different bodies means that the resolution of complex issues raised by research in developing countries continues to be challenging.
- 1.4 In 2002, the Nuffield Council on Bioethics published the Report, *The ethics of research related to healthcare in developing countries*. It concluded that externally funded research in developing countries is crucial but must be subject to rigorous ethical safeguards to prevent the exploitation of those who take part. Rather than setting out guidelines, the Report provides an ethical framework for those designing or conducting externally sponsored research in the developing world.
- 1.5 The Council held a follow-up Workshop in February 2004, co-hosted with the Medical Research Council (MRC) of South Africa, to explore the practical implications of new and recently revised guidelines since the publication of the 2002 Report. The Workshop provided an opportunity for researchers, sponsors and members of ethics committees from developed and developing countries to exchange experiences, and to consider how the guidelines may be applied in practice, particularly when they provide conflicting advice. Fifty-eight delegates from 28 countries attended the meeting. Further details about the Workshop, the programme and a list of delegates can be found in Appendix C.
- 1.6 This Discussion Paper identifies areas of concern arising from recent developments in the guidelines and draws out general themes from the discussion. It does not reconsider specific ethical issues addressed in the 2002 Report. Some background knowledge of the issues related to research in developing countries is assumed; a bibliography for those new to the issues is given in Appendix D.

Structure of the Paper

- 1.7 This Paper begins with a brief overview of a number of guidelines, regulations, declarations and recommendations that have been newly established or revised since 2002 (see Table 1.1). Most are only persuasive and do not have the force of law. We refer to them collectively as 'the guidance'. Chapters 2–5 report the discussion of four topics at the Workshop: consent, standards of care, what happens after the research is over, and ethical review. These topics are often interrelated, but are treated separately here for ease of reference. Each chapter starts with a summary of relevant guidance that highlights areas of agreement and disagreement, and then provides details of the participants' own experiences and concerns raised during the Workshop.
- 1.8 Chapter 6 was drafted by the Steering Committee following discussion at the Workshop. It draws together some of the general themes that were identified during the meeting, including community participation, the development of expertise, sustainability, partnership and ensuring feedback from research. Issues requiring further discussion are also identified, including those raised by chronic diseases, research on public health, and intellectual property. A discussion of the importance of defining research priorities follows. Finally, in light of the discussion at the Workshop, we consider the status of the Declaration of Helsinki, and its practical implementation. It should be noted that not all of the views reported in the Paper were necessarily shared by all of the delegates or the Nuffield Council.

Overview of the guidance

- 1.9 When planning research in developing countries, researchers and sponsors may have to refer to:
- international guidelines or conventions;
 - European Union Directives;
 - national laws or guidelines;
 - regulations and guidelines for research sponsored by the pharmaceutical industry;
 - guidelines produced by funding agencies;
 - institutional guidelines;
 - guidelines relating to a specific disease; and
 - recommendations from advisory bodies.
- 1.10 Since it was first published in 1964, the Declaration of Helsinki has been regarded by many as the pre-eminent guidance on the ethics of research related to healthcare. The Declaration established a set of fundamental principles from which were derived some general rules of conduct for research. Since 1964, it has been revised five times by the WMA, most recently in 2000 (WMA 2000). Paragraphs 29 (standards of care) and 30 (after the research is over) were discussed and clarified in 2002 and 2004 respectively (see Box 4.1).
- 1.11 In 1982, CIOMS, in collaboration with the WHO, published guidelines to address the special circumstances that arise when applying the Declaration of Helsinki to research undertaken in developing countries. The CIOMS guidelines were revised in 1991, 1993 and in 2002. EU 2001, EGE 2003, and CoE 2004 have all been established relatively recently.
- 1.12 An additional set of regulations and guidelines are in place to provide technical standards for research sponsored by the pharmaceutical industry. For example, the International Conference on Harmonisation (ICH) *Harmonised Tripartite Guidelines: Guideline on Good*

Table 1.1: Guidance considered in the Paper¹

Guidance	Status	Abbreviations in Paper
World Medical Association (WMA): <i>Declaration of Helsinki</i> as last revised in Oct 2000; Note of Clarification on Paragraph 29, Dec 2002; Workgroup Report on the revision of Paragraph 30, Sep 2003; and Note of Clarification on Paragraph 30, October 2004.	Not legally binding, but referred to in other forms of guidance and regulation	WMA 2000
The Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO): <i>International Ethical Guidelines for Biomedical Research Involving Human Subjects</i> , as last revised in Sep 2002.	Not legally binding	CIOMS 2002
Council of Europe (CoE): <i>Additional Protocol to the Convention on Human Rights and Biomedicine concerning Biomedical Research</i> , prepared by the Steering Committee on Bioethics (CDBI) of the Council of Europe adopted by the Committee of Ministers, June 2004. (A draft Protocol, approved by the CDBI in June 2003, was discussed during the Workshop in February 2004.)	Legally binding (if signed and ratified) ²	CoE 2004
European Council and European Parliament (European Union): <i>Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use</i> , April 2001, adopted by Member States by May 2003, brought into force May 2004.	Incorporated into national law for EU Member States; applies within the EU and for multi-centre clinical trials taking place in Member States and other countries	EU 2001

Continued

¹ Discussion at the Workshop and in this Paper considers guidance that has been newly established or revised since 2002. Some of these documents have been finalised since the Workshop, for example WMA 2000, paragraph 30 and CoE 2004. In these cases, the draft versions were referred to at the meeting. In this Paper, we refer to the final versions, which for our purpose, do not differ significantly from the draft documents.

² The Protocol is only binding for those countries that have signed and ratified it, and are party to the 1997 *Convention on Human Rights and Biomedicine*. Nineteen countries have signed and ratified the Convention thus far: Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Georgia, Greece, Hungary, Iceland, Lithuania, Moldova, Portugal, Romania, San Marino, Slovakia, Slovenia, Spain and Turkey. The Council of Europe includes all members of the EU in its membership as well as other non-EU European countries.

Table 1.1: Guidance considered in the Paper (Continued)

Guidance	Status	Abbreviations in Paper
The European Group on Ethics in Science and New Technologies (EGE): <i>Opinion Nr 17 on the ethical aspects of clinical research in developing countries</i> , published in Jan 2003.	Advisory	EGE 2003
Nuffield Council on Bioethics: <i>The ethics of research related to healthcare in developing countries</i> , April 2002. ³	Advisory	NCOB 2002

Clinical Practice (1996) provides unified technical standards for clinical trials so that clinical data are mutually acceptable to regulatory authorities in the EU, US and Japan.⁴

- 1.13 Some organisations have devised their own guidelines to address ethical issues raised by research in developing countries, or related to a specific disease. For example, the Joint United Nations Programme on HIV/AIDS (UNAIDS) has published guidelines for researchers conducting research on vaccines for HIV/AIDS.⁵ Funding agencies, including the UK Medical Research Council (MRC), the Wellcome Trust and the National Institutes of Health (NIH), that sponsor healthcare-related research in developing countries have also produced guidelines for researchers.⁶
- 1.14 In recent years, some of the guidelines listed in Table 1.1 have been criticised. Critics argue that they are too general to address many of the specific and often controversial issues that are raised by research. For example, guidelines about the standards of care that should be provided to those participating in clinical trials, and the level of medical care that should be provided after a trial is over tend to be set out in very general terms and have been subject to varied and contradictory interpretations.⁷ Furthermore, these guidelines are not consistent in the advice that is given. Nor do they always take into account the special circumstances that may attend externally funded research undertaken in developing countries.

³ Whereas the other documents listed in Table 1.1 provide specific guidelines on externally sponsored research, this Report focuses on establishing an ethical framework for those conducting such research, and provides recommendations.

⁴ ICH is a project that brings together the regulatory authorities of Europe, Japan and the US and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. The purpose is to make recommendations on ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines. See also ICH (1997) *Technical Requirements for Registration of Pharmaceuticals for Human Use*, and WHO (1995) *Guidance on Good Clinical Practice for Trials on Pharmaceutical Products*.

⁵ UNAIDS (2000) *Ethical Considerations in HIV Preventive Vaccine Research* (Geneva: UNAIDS).

⁶ Medical Research Council UK (2004) *MRC Ethics Guide: Research involving human participants in developing societies* (London: MRC); Wellcome Trust (2005) *Wellcome Trust Funded Research Involving People Living in Developing Countries* (London: Wellcome Trust); NIH (1997) *Guidelines for the conduct of research involving human subjects at the NIH* (5th Printing August 2004) (Washington, DC: NIH). The NIH guidelines apply to research sponsored from within the US but carried out elsewhere. See also National Bioethics Advisory Commission (2001) *Ethical and Policy Issues in International Research: Clinical trials in developing countries* (Bethesda: NBAC), which was published prior to the Report of the Nuffield Council on Bioethics (2002) *The ethics of research related to healthcare in developing countries*.

⁷ NCOB 2002, paragraphs 5.3–5.4.

- 1.15 Despite these difficulties, the consideration of suitable guidance and a rigorous process of ethical review can help those designing or conducting research to address the issues that are raised. However, even the best possible guidance would not necessarily resolve them. In the following chapters, we discuss applications of the guidance listed in Table 1.1, and the problems that may be encountered in four important areas for healthcare-related research: consent, standards of care, what happens after the research is over, and ethical review. In each chapter, the issues are first examined in the light of international guidance, and secondly, in the context of discussions at the Workshop. Tables comparing relevant provisions of the guidance, based on a Background Paper that was circulated to all Workshop delegates, are provided at Appendix A.

Chapter

Consent

2



Consent

Introduction

- 2.1 The importance of obtaining informed consent from individuals who take part in research has been widely recognised. Individuals giving consent must be informed of the potential risks and benefits of participating in research. If they take part, they must do so voluntarily. In the case of research involving minors or individuals without the mental capacity to consent, consent can be given by a person authorised to do so on their behalf. When externally sponsored research is conducted in developing countries, a range of additional issues may arise when consent is sought from potential participants. For example, in some communities it is customary for male members of the family to make decisions on behalf of wives and children. There will often be a tension between the duty of the researcher to be sensitive to cultural differences, and the duty to ensure that each individual has consented to participate in research.
- 2.2 The way in which information on the potential risks and benefits of research is provided is particularly important when participants are from developing countries. Those approached to participate may lack familiarity with basic practices of medical research, such as the use of clinical trials to test new treatments. Views about the causation of illness may differ from the 'western' medical model. Researchers must do their best to communicate information accurately and in an intelligible and appropriate way, taking account of local knowledge and beliefs. There are also questions about the type of documentation that is suitable for use in communities where many lack literacy. In such situations, it may be inappropriate to ask participants to sign consent forms. Witnessed verbal consent might be used instead.
- 2.3 Participants in research are likely to have a range of motivations for taking part. In developing countries some may agree to participate because they believe it may be their only means of receiving improved healthcare or other benefits. There is a potential conflict between the dual roles of healthcare practitioners who simultaneously provide healthcare and recruit research participants. The process of gaining informed consent must therefore be carefully designed.¹
- 2.4 In the Workshop, four issues were considered:
 - who should give consent?
 - provision of information;
 - recording consent; and
 - inducements to take part in research.

Who should give consent?

Guidance

- 2.5 There is general consensus in the guidance that, in the majority of cases, informed consent must be obtained from potential research participants.² In addition to individual consent, some guidance (CIOMS 2002, EGE 2003 and NCOB 2002) also requires investigators to respect cultural traditions by consulting the community or 'senior family members' when

¹ For further information about consent and the ethics of healthcare-related research see NCOB 2002, Chapter 6.

² Exceptions to the general requirement for informed consent include epidemiological research activities that entail monitoring for public health by using, for example, surplus human tissue.

appropriate³ (see Appendix A, Table 1). Such ‘community consent’ may be crucial in specific cases, although the guidance is unanimous that it must be in addition to, rather than instead of, properly informed individual consent.

Workshop discussion

- 2.6 During discussion, delegates reaffirmed that where community consent was sought, it should be in addition to genuine, voluntary consent by individuals (see Box 2.1).⁴ Community consent could have several purposes. It could be used as a form of consultation with the community before individuals are approached, as a method of obtaining ‘permission’ from leaders, and as an additional means of providing information. Indeed, consultation with the community as a complementary activity was often likely to be crucial. Understanding the social and cultural context in which research was being conducted was essential, and involving the community demonstrated respect for local traditions. In addition, it was suggested that, on many occasions, informing and consulting with the community had been proved to be the most effective means of aiding understanding and helping to ensure that consent was genuine. (See paragraphs 2.9–2.16 for further discussion about the provision of information for informed consent.)

Box 2.1: Genuine consent

The concept of ‘genuine consent’ was introduced by the Council in 1995 in the Report *Human tissue: ethical and legal issues*. In this Report, the Council concluded that ‘the ethically significant requirement is not that consent be complete, but that it be genuine’ (paragraph 6.20). This concept was further discussed in NCOB 2002 (paragraphs 6.4–6.8). Since description can never be fully exhaustive, consent will always be an action that is incompletely described; moreover the descriptions given may often be incompletely understood. This incompleteness cannot be remedied by devising more elaborate consent forms. Fully informed consent is therefore an unattainable ideal. Obtaining genuine consent requires medical practitioners to do their best to communicate accurately as much as patients, volunteers or relatives can understand about procedures and risks, and to react to the limits of their understanding, and of their capacities to deal with difficult information. If all reasonable care is exercised, adequate and genuine consent may be established, although it will necessarily fall short of fully informed consent. Ensuring that consent is genuine requires care in detecting and eliminating lack of consent. The apparent genuineness of consent can be defeated by a number of circumstances, including coercion, deception, manipulation, deliberate misdescription of what is proposed, lack of disclosure of material facts or conflicts of interest.

- 2.7 However, it was observed that in practice, obtaining consent was often not straightforward. Researchers had experienced a range of problems which could not be resolved by recourse to current guidance. One such example involved a clinical trial of anti-malarial treatment in Malawi (see Box 2.2). Treatment of patients with acute disease in a hospital-based trial had raised particular difficulties. The need for immediate treatment meant that there was often little opportunity to discuss research with potential participants and to give them adequate time for reflection before seeking consent. The patient or guardian might also be very distressed. It was suggested that in these circumstances, consent forms must be particularly clear and brief, and that it might be helpful to continue to provide information after emergency care had been initiated. It was suggested that provision of information before a trial started would enable the community to be involved, and allow potential participants to consider the issues in

³ CIOMS 2002, Commentary on Guideline 4; EGE 2003, paragraph 2.7; NCOB, paragraph 6.22.

⁴ See also NCOB 2002, p77 Box 6.4.

advance (see paragraph 2.14). However, it was often difficult to consult with the relevant community, which might include the entire catchment area of a hospital. This approach would involve contacting large numbers of villages in an area near a hospital, which would be impractical and require significant resources that were unlikely to be available.

Box 2.2: Difficulties in obtaining consent in emergency situations – clinical trial of antimalarial treatment (case study contributed by Professor Malcolm Molyneux)

In Malawian villages, many children die of malaria without even reaching hospital. This is due partly to a lack of sophisticated equipment to treat children who are unconscious or unable to drink, and partly to a lack of transport to take patients to a health facility where appropriate treatment could be provided.

A research study was designed to determine whether the use of artesunate suppositories could provide immediate initial treatment for children suspected to have severe malaria, before they were transported to a larger health facility. Artesunate suppositories could be easily stored and administered by unskilled people without sophisticated equipment.

An initial trial was conducted in Blantyre to test whether artesunate was adequately absorbed from the rectum in children with severe malaria. The study, which was conducted in a hospital, involved children admitted with 'moderately severe' malaria. Parental consent was sought for eligible children. Of those enrolled in the trial, four in five received rectal artesunate, and a small control group were given the standard intravenous therapy (quinine).

The process of obtaining consent was not straightforward. The consent form was very complex, with two full pages of text. Researchers found that it was unrealistic to aim to convey this amount of information to a mother with a semi-conscious child. In addition, treatment needed to begin promptly, which meant that the time for explanation, reflection and consultation was limited. Although consent was taken by a nurse in the patient's language, there was also a problem with translation and interpretation of terms such as 'randomisation' and 'drug absorption'.

See Barnes KI, Mwenechanya J, Tembo M, McIlleron H, Folb PI, Ribeiro I, Little F, Gomes M and Molyneux ME (2004) Efficacy of rectal artesunate compared with parenteral quinine in initial treatment of moderately severe malaria in African children and adults: a randomised study *Lancet* **363**:1598-605.

2.8 Other points that were made when considering who should give consent included:

- Particular safeguards may be needed when consent is requested for children (see Boxes 2.2 and 2.3), the mentally incapacitated, and those who are unconscious.
- Obtaining consent in large-scale emergency situations where rapid intervention is required may also be difficult. Examples included situations where research had been conducted on patients with acute disease in refugee camps or during major epidemics. Undertaking a trial of a medicine during a major epidemic of cerebrospinal meningitis was one such case.
- Community randomised trials may raise different issues. For example, in an evaluative study, a new treatment is sometimes made available in health centres in selected communities, and its effects are compared with those in communities not given access to the treatment. In such circumstances it would be important and appropriate to seek the consent of the communities to be included in such a study before decisions are made about which health centres should be included in the trial. While it is clearly appropriate to seek individual informed consent from those offered the new treatment in the communities in which it was introduced (those refusing would be offered the standard treatment), it is unclear whether individuals should be asked to give informed consent in

the communities in which the new treatment was not made available.

- CIOMS 2002 is the only guidance to explicitly allow for the possibility of waiving the process of obtaining consent, when the research carries no more than a minimal risk, and the procedures involved do not usually require signed consent forms.⁵ Delegates considered that waiving of consent should only be considered in exceptional circumstances.

Box 2.3: **Consent for children – HIV vaccine trials (case study contributed by Ms Catherine Slack)**

HIV vaccine trials in South Africa (SA) currently involve adults who are able to give consent for participation. However, in some situations there is also a high risk of infection for children. Trials to provide data on safety, immunogenicity and efficacy of preventive HIV vaccines among children are therefore required and issues of consent for children to take part need to be addressed.

Current SA Medical Research Council (MRC) Guidelines allow parents to give consent for their children to participate in research classified as 'non-therapeutic' only where it is observational and of 'negligible' risk.* It is likely that early trials of HIV vaccines will be seen as non-therapeutic but unlikely that HIV vaccine research would fulfil criteria for observational research of negligible risk. Current MRC Guidelines therefore run the risk of excluding children from such trials.

New guidance has therefore been drafted in specific SA MRC Guidelines on HIV vaccine research.† This allows adults to consent to the participation of children in research provided that:

- the research could not be carried out with less vulnerable participants in the trial;
- the purpose is to obtain knowledge relevant to the health needs of children;
- the risks from procedures that do not hold out direct health-related benefit are comparable to those from routine medical or psychological tests;
- the risks from procedures that do hold out direct health-related benefit are justified by the benefit; and
- legal and ethical requirements for consent and assent are met.

* Medical Research Council of South Africa (2002) *Book 1 Guidelines on ethics for medical research: General principles* (SA MRC).

† Medical Research Council of South Africa *Book 5 Guidelines on ethics for medical research: HIV vaccine trials* (SA MRC).

Provision of information

Guidance

2.9 There is unanimous agreement in the guidance that each research participant must be adequately informed about the 'nature, significance, implications and risks' associated with a research trial⁶ (Appendix A, Table 1). However, the guidelines vary in the degree of detail that they recommend should be provided to participants. CIOMS 2002 provides the most comprehensive advice. Guideline 5 lists 26 essential features of the research that must be

⁵ CIOMS 2002, Guideline 4.

⁶ WMA 2000, paragraph 22; CIOMS 2002, Guideline 4; CoE 2004, Article 14; EU 2001, Article 3, 2(d); EGE 2003, paragraph 2.7; and NCOB 2002, paragraph 6.22.

addressed during the consent process, including the design of the research (e.g. randomisation, double blinding); possible health risks for participants and treatment options; issues relating to data protection; and questions of liability in the case of disability or death resulting from injury related to the research (see also Box 2.4).

- 2.10 While the provisions of most guidelines focus on issues relating to recording consent, some explanatory notes emphasise the significance of the consent process itself.⁷ They stress the importance of developing methods to help participants understand the implications of taking part in research (see Box 2.1).

Workshop discussion

- 2.11 Several delegates commented that consent forms often appeared to be designed to protect researchers and their sponsors rather than participants. The forms were frequently too long and complex, making them inaccessible to participants. Examples included a consent form for trials of a rotavirus vaccine in India which was nine pages in length. Although the form had been translated into the local language, its content was considered to be too technical for participants to understand. Many potential participants remained confused about both the purpose of the vaccine and the trial. In another example, a consent form for a trial of a meningococcal vaccine in northern Ghana was 14 pages in length. Despite protracted discussion with the sponsors, it had not proved possible to simplify the contents of the form for legal reasons.
- 2.12 Another problem can arise when consent forms developed for a specific project are adapted without adequate understanding of local knowledge, which may lead to misinterpretation. For example, it was reported that in Kenya a consent form designed in English and translated into the local language was found to have misinterpreted essential information when it was back-translated. Many languages will not have corresponding terms for words such as 'placebo' and particular care is needed if the research is to be explained successfully.
- 2.13 It was suggested that the essential information for a participant to understand should be identified when a consent form is being drafted. The challenge is to provide clear and concise information which informs the prospective participants without overwhelming or misleading them. Delegates concluded that it was unrealistic to fulfil the 26 requirements for consent set out in the CIOMS guidelines in the consent form itself. Instead, it would be more appropriate to provide a consent form of no more than one page, with essential information contained in a few accessible statements. Additional details could then be provided in an information sheet which would be given to participants to read, or have read to them, at home, before consent was sought. The information in the sheet could also be conveyed to participants in advance of the study through public meetings with the community or by using other methods of explanation, such as illustrations. Some information, relevant only to the ethical review of the study, might be included in the study protocol. A proposal, developed by delegates in the Breakout Groups (see programme, Appendix C) is given in Box 2.4.

⁷ CIOMS 2002, Commentary on Guideline 4; CoE 2004, Explanatory Report, paragraph 72.

Box 2.4: Proposal for providing information to prospective research subjects prior to obtaining consent to participate in research

The 26 CIOMS 2002 requirements for consent are divided below into three groups. They are: those for inclusion in the consent form; those for inclusion in the information sheet, and those for possible inclusion in the research protocol for submission to appropriate research ethics committees (numbers in brackets refer to the list of requirements in CIOMS 2002, Guideline 5 (1-26)).

Information in consent form	Information in additional information sheet	Information in research protocol
that the individual is free to refuse to participate and will be free to withdraw from the research at any time without penalty or loss of benefits to which he or she would otherwise be entitled; (2)	for controlled trials, an explanation of features of the research design (e.g., randomization, double-blinding), and that the subject will not be told of the assigned treatment until the study has been completed and the blind has been broken; (4)	that the individual is invited to participate in research, the reasons for considering the individual suitable for the research, and that participation is voluntary; (1)
the purpose of the research, the procedures to be carried out by the investigator and the subject, and an explanation of how the research differs from routine medical care; (3)	whether money or other forms of material goods will be provided in return for the individual's participation and, if so, the kind and amount; (6)	whether the investigator is serving only as an investigator or as both investigator and the subject's physician; (21)
any foreseeable risks, pain or discomfort, or inconvenience to the individual (or others) associated with participation in the research, including risks to the health or well-being of a subject's spouse or partner; (9)	the expected duration of the individual's participation (including number and duration of visits to the research centre and the total time involved) and the possibility of early termination of the trial or of the individual's participation in it; (5)	the limits, legal or other, to the investigators' ability to safeguard confidentiality, and the possible consequences of breaches of confidentiality; (15)
the provisions that will be made to ensure respect for the privacy of subjects and for the confidentiality of records in which subjects are identified; (14)	that, after the completion of the study, subjects will be informed of the findings of the research in general, and individual subjects will be informed of any finding that relates to their particular health status; (7)	
	that subjects have the right of access to their data on demand, even if these data lack immediate clinical utility (unless the ethical review committee has approved temporary or permanent non-disclosure of data, in which case the subject should be informed of, and given, the reasons for such non-disclosure); (8)	
	any foreseeable risks, pain or discomfort, or inconvenience to the individual (or others) associated with participation in	

Continued

Box 2.4: (Continued)

Information in consent form	Information in additional information sheet	Information in research protocol
the possible research uses, direct or secondary, of the subject's medical records and of biological specimens taken in the course of clinical care, and details about their storage and possible future use if relevant; (18 and 19)	the research, including risks to the health or well-being of a subject's spouse or partner; (9) (see also <i>Information in Consent Form</i>)	
	the direct benefits, if any, expected to result to subjects from participating in the research; (10)	
	the expected benefits of the research to the community or to society at large, or contributions to scientific knowledge; (11)	
that treatment will be provided free of charge for specified types of research-related injury or for complications associated with the research, and details about the provision of such treatment; (23)	whether, when and how any products or interventions proven by the research to be safe and effective will be made available to subjects after they have completed their participation in the research, and whether they will be expected to pay for them; (12)	
	any currently available alternative interventions or courses of treatment; (13)	
If relevant: policy with regard to the use of results of genetic tests and familial genetic information, and the precautions in place to prevent disclosure of the results of a subject's genetic tests to immediate family relatives or to others (e.g., insurance companies or employers) without the consent of the subject; (16)	the sponsors of the research, the institutional affiliation of the investigators, and the nature and sources of funding for the research; (17)	
	whether commercial products may be developed from biological specimens, and whether the participant will receive monetary or other benefits from the development of such products; (20)	
	the extent of the investigator's responsibility to provide medical services to the participant; (22)	
	in what way, and by what organization, the subject or the subject's family or dependants will be compensated for disability or death resulting from such injury (or, when indicated, that there are no plans to provide such compensation); (24)	

Continued

Box 2.4: (Continued)

Information in consent form	Information in additional information sheet	Information in research protocol
	whether or not, in the country in which the prospective subject is invited to participate in research, the right to compensation is legally guaranteed; (25)	
	that an ethical review committee has approved or cleared the research protocol. (26)	

Summary

A consent form should contain the following information:

I consent to take part in ...

I understand that I am free to withdraw from the research at any time without penalty (2)

It has been explained to me that the purpose of the research is... (3)

And that the risks involved are.... (9)

I understand that the confidentiality of my records will be maintained by ... (14)

It has been explained to me what will happen in the event of injury or complications (23)

I have had the opportunity to ask questions

If appropriate: The policy with regard to the use of genetic tests has been explained to me (16)

I understand that x, y and z will happen to any biological samples collected during the course of the research (18, 19, and 20).

- 2.14 Creative and cost-effective methods of communication may also be required. Communities could be made aware in advance, by using the press, radio and television, by making 'information packs' available, or by holding community seminars. Other examples cited included the use of dance troupes and school plays to convey information (see also Box 2.5). The process of informing participants should continue after enrolment, allowing time for further explanation, reflection and consultation. It might also be helpful for participants to have the opportunity to discuss the trial on more than one occasion, before making a decision on whether to take part.⁸
- 2.15 Community leaders and representatives, and individual participants, must be able to trust the process of consent. It was suggested that members of the community, rather than just the principal investigator, could also be involved in the process of obtaining consent. However, other delegates were concerned that this step might lead to community leaders having undue influence over recruitment. Delegates agreed that field workers and assistants needed to be trained so they could respond to questions about the research that may be posed by participants.
- 2.16 Methods to assess whether participants have properly understood the nature of the research

⁸ This option would not apply to trials of treatment for acute life-threatening illness.

Box 2.5: Obtaining informed consent – Kenya AIDS Vaccine Initiative (KAVI) (case study contributed by Dr Job Bwayo)

Trials to evaluate the safety and immunogenicity of a candidate HIV vaccine were held for the first time in Kenya in 2000. The recruitment rate was initially slow and so measures were put in place to improve awareness of the trials in the community. They included:

- Community representatives were given training to enable them to initiate discussions about the purpose, benefits and risks of the research.
- A range of informal community seminars were held. Scientists were invited to ‘talk science’ to the community in a language that was well understood.
- Interested individuals were invited to attend formal seminars at an evaluation unit, which included the opportunity to participate in question and answer sessions with the researchers.

Measures were also put in place to help ensure that those who were interested in participating had understood the nature of the research:

- Those who wanted to join the trial attended at least three one-to-one counselling sessions before being considered for entry.
- Before potential volunteers were entered into the trial, they took a test to assess their understanding. A minimum score of 80% was required before an individual could be invited to consent to participate.
- Eligible volunteers were given the option to proceed to enrolment or to withdraw their consent, either at this stage or at any other time during the research.

The involvement of the community improved the recruitment of volunteers and the rate of retention. It also enhanced community ownership of the process of vaccine development.

Wakasiaka S, Bwayo JJ, Ndinya JA, Jaoko WG, Omu A, Omosa G M, Ogutu HA and Nyange J (2004) Enhanced volunteer recruitment in HIV vaccine trials in Kenya XV *International AIDS Conference 11-16 July 2004 Bangkok, Thailand* Conference Abstract number: ThPeA6999. Available: http://www.iasociety.org/ejias/show.asp?abstract_id=2170240 Accessed on: 25 Feb 2005.

in which they are participating were also considered. It was suggested that a separate team, again appropriately trained, may be required to monitor consent. Monitoring should aim to assess the participants’ general understanding of the implications of the trial rather than test their retention of information with a check list of facts. It was noted that monitoring would be a valuable addition to many trials conducted in developed countries, where participants may have an incomplete understanding of the implications of their participation.

Recording consent

Guidance

2.17 The guidance differs with respect to the acceptability of different methods of documenting consent to participate in research (Appendix A, Table 1). EGE 2003 does not indicate how consent should be recorded, while WMA 2000, CIOMS 2002, CoE 2004 and NCOB 2002 recommend that researchers should obtain written consent when appropriate. When written consent is not feasible, WMA 2000, CIOMS 2002, CoE 2004, EU 2001 and NCOB 2002 state that verbal consent is acceptable, provided that it is formally documented and witnessed.⁹ EU 2001 specifies illiteracy as a necessary condition for permitting verbal consent.

⁹ WMA 2000, paragraph 22; CIOMS 2002, Commentary on Guideline 4; CoE 2004, Explanatory Report, paragraph 79; EU 2001, Article 3.2 d; NCOB 2002, paragraphs 6.37–6.40.

Workshop discussion

- 2.18 It was suggested that there is too much emphasis on 'written' consent in the guidance. For example, in Mexico, national regulations specify that 'valid informed consent' must be obtained before research begins and that the consent form must be signed by the participant and two witnesses.¹⁰ Researchers have found that this requirement creates some difficulties. The presence of additional people during the consent process may cause discomfort for the participant and limit confidentiality. One of the witnesses will often be the study coordinator, but providing a second witness may be more difficult. Investigators will often ask participants to attend with a relative, who can act as a witness and support the participant during the research. However, when the accompanying relative is a man, he may be very influential and inhibit a woman from deciding for herself whether or not to participate. An additional complication is that some sponsors will not accept family members as witnesses.
- 2.19 There was general agreement that proper monitoring and documentation of the consent process was more important than whether or not a participant provided written consent. If consent is recorded with a tape recorder, it would be important to ensure that the tape was safely stored and would not deteriorate. Delegates agreed that in many situations, having the consent process witnessed would be more acceptable to participants than providing a signature. For example, in Malawi, trial participants were often concerned that signing may entail unforeseen obligations, such as tax liabilities or trouble with the police.

Inducements to take part in research**Guidance**

- 2.20 CIOMS 2002 recommends that payments to research participants, either in money or in kind, 'should not be so large as to persuade them to take undue risks or volunteer against their better judgment'¹¹ (Appendix A, Table 1). NCOB 2002 comments that inducements to take part in research must be appropriate to the local context and, along with CoE 2004, recommends that they are considered by the local research ethics committee.¹²

Workshop discussion

- 2.21 Where healthcare facilities are lacking, participants may decide to take part in research in order to have access to better care. The availability of treatment during and after a trial might also count as an inducement. Delegates emphasised that while researchers should aim to ensure that participants are not placed in a worse position by participating in research, a decision to participate must be made voluntarily. Care should be taken to ensure that any payment did not become an inappropriate inducement to accept risks that would not otherwise be considered acceptable. It was suggested that guidance should be clearer on the question of payments, including when they should be made and which costs should be covered. The point at which inducements become excessive was not always clear. In many developing countries, \$5 for loss of earnings or for travel costs could be a substantial incentive for individuals to participate. Delegates suggested that, where possible, improvements to healthcare were more appropriate inducements than financial payments (see Box 2.6).

¹⁰ Ley General de Salud (General Law of Health) (Articles 100 and 103) *Rules for research in human beings*.

¹¹ CIOMS 2002, Commentary on Guidelines 3 and 7.

¹² NCOB 2002, paragraph 6.32; CoE 2004, Articles 11 and 12 and Appendix xvi.

Box 2.6: Inducements – the International HapMap project (case study contributed by Professor Charles Rotimi)

An international project, HapMap, was established in 2002 to create a haplotype map of the human genome. The project will describe the common patterns of human DNA sequence variation and may be used to identify genes linked to susceptibilities to disease. Researchers from Canada, China, Japan, Nigeria, the UK and US expect to complete the map by 2005. Participants are asked to donate blood samples so that their DNA can be studied.

Participants in the International HapMap project in Nigeria were each given an equivalent of approximately US \$8.00 and multivitamins worth about US \$4.00 to compensate them for their time and travel. This amount was comparable to the sum given for the donation of blood (for use in the blood transfusion service) in the same region. Prospective donors were only told that they would be compensated after they had arrived to donate blood. This approach was adopted to guard against the possibility that they would be induced to participate by the prospect of material benefit. However, they might have learned of the payment by word-of-mouth.

One community requested assistance to establish a hospital in return for their contribution to the HapMap project. This request raised concerns that community leaders would place undue pressure on people to participate in the research because of the promise of a new hospital. Even if a hospital was provided for the community, it might not be sustainable in the long term. An alternative healthcare benefit for the local community was therefore under consideration.

See The International HapMap Consortium (2003) The International HapMap Project *Nature* 426: 789–96; The International HapMap Consortium (2004) Integrating ethics and science in the International HapMap Project *Nature Reviews Genetics* 5: 467–75.

Summary of discussion on consent

2.22 Several themes emerged during the Workshop. These were:

- The primary purpose of the consent process should be to inform and protect the participant and ensure that he or she understands the reasons for the research and the consequences of taking part.
- This may mean adapting the guidance to fit the local context and will certainly require simple consent forms, supplemented by more detailed information for participants, using appropriate language and explanations.
- It will often be necessary to seek innovative ways of providing information to participants and the process may need to be continued after consent has been given.
- Proper monitoring and documentation of the process is more important than whether the participant provides written consent.
- The trust of the participants in the process is crucial.

2.23 Additional points that are not currently addressed by most guidance included:

- There was some debate as to whether health services and operational research¹³ were adequately covered in the guidance. It was suggested that both individual and

¹³ Health services and operational research are concerned with the study of methods of delivery of healthcare, access to treatment and quality of care, with the aim of finding improved methods that lead to better care. Such studies often include an evaluation of the cost of providing the intervention and the benefit it provides.

community consent should be sought for this type of research. However, this approach is not currently followed in practice and may be difficult to organise.

- Difficult consent issues had arisen when research was conducted primarily for the benefit of the community rather than for individual participants. For example, a trial might be conducted to find out which treatment would be most appropriately supplied through the local health authority, rather than whether one is better than another.
- Particular difficulties had been experienced when obtaining consent from patients with acute disease in hospitals or in emergency situations.
- The guidance tended to be biased towards clinical trials and did not address issues raised in other areas of research such as genetics.

Chapter

Standards of care

3



Standards of care

Introduction

- 3.1 There has been significant international debate about the 'standard of care' that should be provided to participants during research in developing countries. Much of the controversy has focused on the level of care provided to the control group in clinical trials. Two questions are fundamental to the debate. First, should the control group receive the best current treatment available anywhere in the world ('universal standard of care'), or treatment based on the standard available in the local or regional context ('non-universal standard of care')? (See Box 3.1 for a summary of these different terms.) Secondly, is it acceptable to give placebos to a control group if an effective treatment already exists but is not available locally?
- 3.2 Some argue that when research is externally sponsored, participants in developing countries should receive the same standard of care and treatment as participants would receive if the research was conducted in the country of those sponsoring the research. Others argue that the standard of care provided to the control group is a critical component of trial design that affects the scientific value and direction of research (for further discussion see NCOB 2002, p89). They claim that a requirement for a universal standard could prevent research that has the potential to benefit people in developing countries from being undertaken. For example, research which aimed to compare a new treatment with one currently available to the target population might not be possible.
- 3.3 In 1997, clinical trials designed to determine whether short courses of an antiretroviral treatment (ART) for HIV/AIDS could reduce the transmission of the virus from mother to child were criticised for using placebos, rather than the universal standard of care, in the control groups. Longer courses of the treatment were already known to reduce perinatal transmission of the virus but the trials were conducted in countries where local care did not include access to the medicine. A protracted international debate has not resolved the issue although the some of the guidance has been revised accordingly. The extent of disagreement is reflected in the Background Note to CIOMS 2002, which refers to the 'unresolved or unresolvable conflict' in discussion about the appropriateness of applying a universal standard of care.¹ (See also NCOB 2002, Chapter 7).
- 3.4 Separate issues that are not addressed in the guidance concern the standard of care that should be provided to research participants who develop either the condition(s) being studied or unrelated conditions. What standard of care should be provided to these participants during, or following, the research period? When research into preventive measures is conducted, what standard of care should be offered to patients who develop the disease once the research is completed? These issues are inter-related but require distinct ethical analysis, since it can be argued that obligations to provide treatment differ in each case. For example, the obligations to provide treatment for patients who develop the disease being studied during the trial can be distinguished from the obligations to provide treatment for unrelated conditions.
- 3.5 In the Workshop, four main issues were considered:
 - the standard of care that should be provided to the control group during research;
 - the use of placebos;
 - the obligations of sponsors; and
 - the provision of care to all trial participants.

¹ CIOMS 2002: The controversy is described in more detail in the Commentary on Guideline 11, which addresses *Choice of control in clinical trials*.

Box 3.1: Terms used to describe standards of care

- **WMA 2000:** uses the terms ‘best proven’ or ‘best current’ ‘prophylactic, diagnostic, and therapeutic methods’ when discussing the nature of treatment that should be provided to trial participants. It is not clearly stated that this standard would be the best proven treatment available anywhere in the world but some have interpreted it accordingly (paragraph 29).
- **CIOMS 2002:** ‘For many indications ... there is more than one established ‘current’ intervention and expert clinicians do not agree on which is superior. In other circumstances in which there are several established ‘current’ interventions, some expert clinicians recognize one as superior to the rest; some commonly prescribe another because the superior intervention may be locally unavailable, for example, or prohibitively expensive or unsuited to the capability of particular patients to adhere to a complex and rigorous regimen. ‘Established effective intervention’ [refers] to all such interventions, including the best and the various alternatives to the best’ (Introduction).
- **NCOB 2002:** ‘universal standard of care’ is used to ‘indicate the best current method of treatment available anywhere in the world for a particular disease or condition. For most diseases and conditions, this standard of care is routinely available to only a small proportion of the world’s population’ (Box 7.1).

For the purposes of this discussion we will use the term ‘universal standard of care’ as it is defined by NCOB above; the term ‘non-universal standard of care’ refers to regional and local standards that might entail a lower level of care.

The standard of care that should be provided to the control group during research

Guidance

3.6 The Declaration of Helsinki (WMA 2000, paragraph 29) is interpreted by some to demand provision of a universal standard of care to a control group, regardless of where the research takes place:

‘The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods.’

3.7 However, CIOMS 2002, CoE 2004 and NCOB 2002 acknowledge that in some circumstances, a non-universal standard of care might be permissible² (Appendix A, Table 2). As NCOB 2002 describes:

‘If an aim of research into healthcare is to improve current forms of treatment, then there may be circumstances in which it is justified to compare current local practice with a new treatment, in the local setting.’³

A non-universal standard may be acceptable for trials comparing different standards of care, where the universal standard is not available or feasible, and for investigations of preventive measures. NCOB 2002 specifies that the standard of care must be defined in consultation with those who work within the country and must be justified to the relevant research ethics committees.

² CIOMS 2002, Introduction and Commentary on Guideline 11; CoE 2004, Explanatory Report, paragraph 120; NCOB 2002, paragraph 7.29.

³ NCOB 2002, paragraph 7.30.

Workshop discussion

- 3.8 During discussion, delegates reported that local ethics committees appear to be increasingly sympathetic to the use of regional and local standards as a comparator, rather than a universal standard, for clinical trials. However, decisions about standards of care depended on the context of the research. There was agreement that formulating general advice that could be applied to all situations was difficult (see Box 3.2).
- 3.9 It was also suggested that even if it was not feasible to provide a universal standard of care in developing countries, researchers should aspire to provide as high a standard of care as possible. From this perspective, the guidance could be interpreted as encouraging researchers to move towards the highest attainable standard of care. However, delegates acknowledged that the costs of providing a particular standard of care may not be confined merely to the cost of providing medicines, but may also include the related costs of improvements to the healthcare system and infrastructure (see also Box 3.5).
- 3.10 The following points were also made:
- How should the ‘best proven therapy’ or other standards of care be defined, and by whom?
 - The standard of care to be provided should be discussed in the context of the national system for public health.
 - Some delegates considered that it would not be appropriate to use a universal standard of care for trials intended to assess the best way for a government health department to provide an intervention for a particular disease. For example, some research might compare the standard of care proposed by the government with the actual standard of care. In such situations, using a universal standard as the comparator would not be relevant.

The use of placebos**Guidance**

- 3.11 The guidance generally agrees that placebo-controlled trials are justified when there is no other proven treatment⁴ (Appendix A, Table 2). However, the use of a placebo remains controversial when an effective treatment does exist. In 2002, the WMA published a Note of clarification on the use of placebos stating that, where proven therapy is available, they may be used only ‘for compelling and scientifically sound methodological reasons’ or when the risks to the participants are insignificant and the condition being studied is minor.⁵
- 3.12 CIOMS 2002 diverges from the WMA 2000 by concluding that placebos used in place of an ‘established intervention’ may be ethically acceptable in specific cases. For example, in a country where an established effective intervention is not generally available or affordable, and unlikely to become so in the foreseeable future, research using a placebo may be acceptable in order to develop an affordable intervention specifically for that region.⁶ EGE 2003 and NCOB 2002 are in accord with this provision⁷ (Appendix A, Table 2). The EGE guidelines specify that the use of placebos in a developing country should be regulated by the same principles that would apply in the EU but use of a non-universal standard may be justifiable:

‘An obvious [exception] is when the primary goal of the clinical trial is to try to simplify or

⁴ WMA 2000, paragraph 29; CIOMS 2002, Guideline 11; CoE 2004, Article 23.3.

⁵ WMA 2000, Note of clarification on paragraph 29, December 2002.

⁶ CIOMS 2002, Commentary on Guideline 11.

⁷ EGE 2003, paragraph 2.10; NCOB 2002, paragraph 7.30.

to decrease the costs of treatment for countries where the standard treatment is not available for logistic reasons or inaccessible because of cost.’⁸

Workshop discussion

- 3.13 Some delegates were concerned that controversy over the use of placebos has had a significant impact, not only on research, but also on the wording of national guidance. For example, in Brazil, a placebo may only be used in cases where no proven ‘established effective treatment’ is available.

Box 3.2: Interpretation of the guidelines on standard of care – pneumococcal trials

Pneumococci are bacteria that cause acute respiratory disease, ear infections, meningitis and septicaemia. At least 1 million people a year are estimated to die as a result of infection by these bacteria. The majority of deaths occur in young children and older adults, and the primary cause of death is pneumonia.

Africa bears the greatest burden of childhood pneumococcal disease. The prospect of infant pneumococcal vaccination increased in the 1990s when a large clinical trial was planned to take place in The Gambia. The trial aimed to determine the impact of a pneumococcal vaccine on the frequency of severe infections, and the primary endpoint was to be child survival. The trial was sponsored by NIH under an Investigational New Drug (IND) agreement with the US Food and Drug Administration (FDA), together with the US Agency for International Development (USAID) and the Bill and Melinda Gates Children’s Vaccine Program. Ethical review was provided by committees in The Gambia and the UK, as well as the WHO in Geneva. An international Data and Safety Monitoring Board monitored safety data. An individually randomised controlled trial was approved: one group of children would receive the DTP-Hib combination vaccine (for diphtheria, tetanus, pertussis and *Haemophilus influenza* type B) mixed with the pneumococcal vaccine at 6, 10 and 14 weeks of age, while the control group would receive the DTP-Hib vaccine mixed with an inert ‘placebo’.

In February 2000, a pneumococcal vaccine was licensed for use in US infants. Bacterial antigens from seven different pneumococcal serotypes were used to produce the 7-valent vaccine. These seven serotypes cover 85% of disease in the US. However, in developing countries two additional serotypes, types 1 and 5, are prevalent. For the trials in The Gambia and South Africa, the company manufacturing the vaccine produced a 9-valent vaccine that included these two additional serotypes.

The trial in The Gambia started in August 2000. After it was well underway, the company decided to cease production of the DTP-Hib combination that was used to dilute the non-licensed 9-valent study vaccine. Existing supplies were sufficient for the enrolment of only half of the original sample of participants. A modified design to maintain the original sample size, was prepared. However, informal dialogue with US government officials indicated that it was likely that the modified trial would not be considered to be in compliance with the 2000 Revision of the Declaration of Helsinki. This was because the design did not allocate the new 7-valent pneumococcal conjugate vaccine which was by then licensed for use in the US, to the control group. Consequently, the modified design was dropped and not formally submitted to FDA.

Continued

⁸ EGE 2003, paragraph 2.10.

The original trial design was modified again to account for the limited availability of the DTP-Hib vaccine. The sample size of the trial was reduced which meant that there was insufficient statistical power to make child survival the primary endpoint. It was therefore formally changed to the incidence of radiologically proven pneumonia. The trial with the smaller sample size is now complete, and the results will be reported soon.

A literal interpretation of the Declaration of Helsinki, by officials far removed from the setting in which the trial was being conducted, potentially reduced its value by compromising examination of its initial primary end-point, child survival, which would be of greatest relevance in deciding the future public health value of the vaccine.

- 3.14 Whether or not the use of a placebo is acceptable will depend on the nature of the disorder and the prevailing health care system. For example, when a treatment for onchocerciasis (river blindness) was being assessed in a clinical trial in the mid-1980s, the use of a placebo could be justified. At the time, two medicines were regularly used to treat onchocerciasis, diethylcarbamazine (DEC) and suramin. As both could cause frequent and often serious side effects, their use was restricted to selected patients. When clinical trials of a new medicine (ivermectin) were planned, a placebo rather than the local 'standard of care' was used because participants receiving either DEC or suramin could have been harmed. This approach was supported by the results from smaller scale pre-clinical trials (Phase I and II) which compared both ivermectin and DEC against a placebo. These demonstrated that ivermectin was as effective, and much safer, than DEC.⁹ However, in trials of a treatment for malaria, the use of a placebo is unlikely to be acceptable because the disease could be fatal if left untreated. Delegates agreed that use of placebos would have to be considered on a case by case basis.
- 3.15 Other situations in which it was suggested that the use of a placebo might be acceptable included:
- the treatment of non-infectious diseases, especially when the disease itself is of a mild and not permanently incapacitating nature, such as headache;
 - a treatment being re-tested to account for regional variation in efficacy; and
 - the treatment of acute diseases where the standard of care available in developed countries was not easy to attain in the health system settings of developing countries. In addition, where the use of that standard of care would preclude the possibility of detecting effects of interventions that were better than existing therapy but not as effective as the treatment available in developed countries.

The obligations of sponsors

Guidance

- 3.16 With regard to the provision of care, most of the guidance does not address the obligations of sponsors (Appendix A, Table 2). However, EGE 2003 states that where research participants do not receive a standard treatment of care because of the cost, it must be provided by the sponsor.¹⁰

⁹ For details of formal control trials of ivermectin against DEC see Awadzi K, Dadzie KY, Schulz-Key H *et al.* (1986) The chemotherapy of onchocerciasis. XI. A double-blind comparative study of ivermectin, diethylcarbamazine and placebo in human onchocerciasis in northern Ghana *Ann Trop Med Parasitol* **80**: 433-42; Dadzie KY, Bird AC, Awadzi K *et al.* (1987) Ocular findings in a double-blind study of ivermectin versus diethylcarbamazine versus placebo in the treatment of onchocerciasis *Br J Ophthalmol* **71**: 78-85.

¹⁰ EGE 2003, paragraph 2.12.

Workshop discussion

- 3.17 The requirement that sponsors should meet the costs of a higher standard of care than the best available as part of a national health system may have far reaching implications. There were fears that some funding agencies would be unwilling to support trials in which such costs were substantial. One suggestion was that sponsors should endeavour to ensure that the standard of care provided was aligned with a healthcare practice that was locally sustainable.
- 3.18 The obligations of sponsors to pay for routine care for all research participants in a trial were also discussed. In South Africa, the MRC Guidelines specify that all participants in trials for HIV-1 vaccines should have access to high quality treatment financed by the sponsors (see Box 3.3). Long-term care of participants who were HIV positive, or who suffered from chronic diseases such as hypertension or diabetes, is also likely to entail significant costs (see Chapter 4). We consider the question of the general provision of care to all trial participants in paragraphs 3.19–3.24.

Box 3.3: Obligations of sponsors – provision of treatment for HIV-1 vaccine trial participants

In South Africa, the Guidelines on HIV vaccine research* specify that:

- trial participants should have access to high quality treatment, and
- this access should be financed by trial sponsors.

Thus, participants who become infected with HIV during vaccine trials should be provided with ART when it is medically indicated. Provision could be achieved by means of a national trust fund managed by a healthcare service provider. Participants who become infected during trials could be issued with an identity card and telephone helpline number. This would provide access to a national network of doctors and practitioners for HIV-related treatment and care from anywhere in the country.

Treatment and care, provided via the trust fund, could be financed by sponsor agencies, who would commit a fixed amount of money for each infected volunteer to cover the costs for at least ten years.[†] Some international agencies have already agreed in principle to the proposed mechanism. However, the approach may not suit low-income countries without an appropriate healthcare infrastructure.

* Medical Research Council of South Africa *Book 5 Guidelines on ethics for medical research: HIV vaccine trials* (SA MRC). These guidelines were compiled by HAVEG (HIV AIDS Vaccines Ethics Group) in collaboration with the Interim National Health Research Ethics Committee (INHREC) and the Medical Research Council of South Africa (MRC).

[†] Tucker T and Slack C (2003) Not if but how? Caring for HIV-1 vaccine trial participants in South Africa *Lancet* **362**: 995.

The general provision of care to trial participants**Guidance**

- 3.19 Questions about the general provision of care that should be provided to participants who require treatment of conditions that are unrelated to the trial are not addressed specifically in the guidance (Appendix A, Table 2). NCOB 2002 recommends that the minimum standard of care that should be offered is the best intervention available as part of the national public health system. Agreement should be reached about what is to be provided before research begins and the proposal should be discussed by the research ethics committee.¹¹

¹¹ NCOB 2002, paragraph 7.35.

Workshop discussion

- 3.20 There was wide support for the general principle that issues relating to standards of care should be discussed before a trial started. Consideration of the level of provision of care was required to allow practical, feasible and innovative solutions to be developed. It was suggested that sponsors should consult closely with local experts and national health authorities (see Box 3.5). However, it was not always clear who should be involved in such discussions, or how they should be initiated.
- 3.21 When considering the level of care to be provided in any setting, delegates agreed that the implications in the longer term should also be considered, with a view to encouraging and ensuring sustainability (see also paragraphs 6.7–6.8). The provision of treatment or the maintenance of a facility after the research is over (see paragraphs 4.12–4.13) were also raised as longer term, but important, considerations. Two particular situations were identified when discussing the level of care to be provided to all participants: the provision of care for conditions related to the trial and the provision of care for other conditions, unrelated to the trial.

The provision of care for conditions related to the trial

- 3.22 Delegates acknowledged that the nature of the disease under study was a crucial determinant of the kind of care that should be provided. Different issues were raised by vaccine trials and trials involving chronic diseases, such as hypertension or diabetes. It was also suggested that changing circumstances may influence what is seen to be ethically acceptable. This was illustrated, for example, by the provision of insecticide-treated nets in trials of a malaria vaccine (see Box 3.4) as nets are now increasingly accepted as routine care. Similarly, the provision of anti-retroviral treatments (ARTs) in HIV intervention trials has been particularly problematic (see Box 3.5), but may become less so as the cost of therapy falls and availability in developing countries improves.

Box 3.4: Provision of care – the changing use of insecticide-treated nets (case study contributed by Professor Brian Greenwood)

Investigators have found it advantageous to conduct trials of vaccines or preventive medicines for malaria without providing participants with insecticide-treated nets (ITNs), since this allows trials to be smaller and cheaper. Until recently, even if provision of ITNs was part of a national policy for malaria control, it was not being implemented in trials. Ethics committees had accepted that it was unnecessary for sponsors to provide ITNs. However, the national malaria control programmes of many malaria-endemic countries are now making strenuous efforts, by means of donations from the Global Fund and others, to increase coverage of ITNs. Although coverage may still be low, the use of an ITN is becoming the routine standard of care. Ethical opinion is moving towards the view that it should be the responsibility of the sponsors to provide ITNs for all participants in malaria-related medicine or vaccine trials. Once a certain level of ITN coverage is reached, the scientific questions being addressed in trials will focus on the impact of a new intervention when used *in addition* to ITNs.

- 3.23 One example discussed by delegates concerned a study in Pakistan that investigated the cause of respiratory tract infections in children who lived in a densely-populated slum. The researchers had to consider questions about the level of treatment that should be given to those found to be infected. The nearest public hospitals had very low standards, and lacked both medicines and facilities for adequate care. The University Hospital where the researchers were based had much higher standards. Should infected children be given the

standard of care of the University Hospital or the local standard of care in their community? The researchers decided that most children with mild illness would be given oral antibiotics. Those requiring hospitalisation would be referred to nearby public hospitals or clinics.

- 3.24 Delegates suggested that, in general, there would be a clear obligation on the researchers to provide care for the condition under study. It was less clear for what length of time care should be provided. In the case of acute disease, the provision of a higher standard of care might be feasible, but treatment of chronic diseases raised particularly difficult questions. Should the obligation last for one year, ten years or a lifetime? Similar questions are posed by the provision of ARTs in HIV intervention trials (see Box 3.5 and Chapter 4).

Box 3.5: Provision of care – HIV intervention trials (case study contributed by Professor Jimmy Whitworth)

The provision of ART is increasingly accepted as the appropriate standard of care for people with symptomatic HIV disease. A number of sponsors conducting HIV vaccine trials have agreed to provide ART for trial participants who become HIV positive during the trial.* For example, the International Aids Vaccine Initiative (IAVI), in its Treatment and Care Policy, has made a commitment to support the provision of ART (when clinically indicated) for participants who become infected during an IAVI trial, for up to five years. The HIV Vaccine Trials Network (HVTN), sponsored by the National Institutes of Health Grants (NIHG) and National Institute of Allergy and Infectious Diseases (NIAID), has developed a strategy for a fund to pay for treatment, and the South Africa Aids Vaccine Initiative (SAAVI) has proposed an insurance scheme (see also Box 3.3). However, it is unclear how these proposals will work in practice, and the approach raises a number of issues:

- Supplying ARTs requires greater commitment than merely purchasing of the medicine. Where there is currently no ART provision in place, it will also be necessary to provide additional infrastructure and improvements in healthcare facilities.
- When a low-technology, low-cost intervention for HIV is evaluated, such as the use of a microbicide or a behavioural intervention, the costs of ART provision would be significantly higher than the costs for the intervention itself. If the provision of ART is required as part of the trial, the cost may be regarded as prohibitive by the sponsors.
- What standard of care should be provided for those who develop HIV during the course of the study? These individuals are not likely to begin to require ART until five years or more after infection, by which time the study is likely to have been completed. Should ART be provided after the end of the study? How can this be arranged?
- What treatment should be provided for individuals found to be already HIV positive when they are screened for entry into a trial? Although they will not be eligible to participate, significant numbers are likely to require ART immediately (as they may have had HIV for some time), potentially increasing the costs of the trial.

It was suggested that researchers should work with local authorities to facilitate the provision of ART. This would encourage a longer term improvement in the provision of healthcare in the region and allow a sustainable approach. It would also reduce concerns about patients being coerced to take part in a trial, because they would be more likely to receive ART locally, regardless of whether they participated.

* Fitzgerald DW, Pape JW, Wasserheit JN *et al.* (2003) Provision of treatment in HIV-1 vaccine trials in developing countries *Lancet* 362: 993–4; Berkley S (2003) Thorny issues in the ethics of AIDS vaccine trials *Lancet* 362: 992.

The provision of care for other conditions

- 3.25 Where a condition unrelated to that directly under study was present in a participant, delegates agreed that a suitable referral to the local health services may be appropriate. However, the mechanism for such a referral would need to be considered in advance and agreed with the local health authorities before the research begins. Particular difficulties may arise if the facilities for appropriate care were not available locally.
- 3.26 An unrelated condition might also be discovered indirectly and not as a direct consequence of research during the course of a trial. It was suggested that in this situation, there may be a lesser obligation on a researcher regarding the provision of care, but a suitable referral should be made. An example was given of a female sex worker in Benin, who was found to have pelvic inflammatory syndrome (resulting from an extra-uterine pregnancy) during a trial of a vaginal microbicide. The patient was referred to a gynaecology clinic, which asked for advance payment before performing an operation. Although this type of situation had not been envisaged when the study was planned, the sponsors agreed to pay the fee for the operation. It was suggested that in situations where the healthcare infrastructure was poor, research teams may be obliged to provide some level of care for all conditions. However, delegates agreed that the extent of this commitment should be assessed on a case by case basis and the approach adopted should be subject to approval from an ethics committee.

Summary of discussion on standards of care

- 3.27 It was clear during discussion at the Workshop that the nature of treatment that should be provided to participants during research remains a particularly controversial issue. Concerns were expressed that, by aiming only for the very best treatment, or a universal standard of care, potentially beneficial research may be prevented.
- 3.28 Several themes emerged throughout the Workshop. These were:
- The use of a regional or local standard of care as a comparator is now seen to be acceptable in some situations, as set out in the guidance of CIOMS 2002, CoE 2004 and NCOB 2002.
 - It is unhelpful to generalise about the standard of care that should be provided, both to the control group and to all participants. Reaching an answer that can be applied in all situations is difficult, but a careful case by case assessment, which acknowledges the limitations of local and regional practicalities, may be useful.
 - Discussion between relevant stakeholders should begin at the planning stage of any trial. Researchers, sponsors, local and national health authorities should work together to ensure acceptable solutions are developed.
 - Controversy over placebos has led to unrealistic requirements in the guidance that might discourage valuable research.
 - Requiring sponsors to meet costs of a universal standard of care may have far reaching implications, some of which may be detrimental to public health.
 - Particular difficulties arise when provision of general care to all participants is contemplated. These issues are not addressed in the guidance.
 - Issues of longer term sustainability should also be considered (see also paragraphs 6.7–6.8). Researchers should try to ensure that improvements in healthcare offered during research are achieved in such a way that the benefits are sustainable after the work is complete.

Chapter

4

What happens once
research is over?



What happens once research is over?

Introduction

- 4.1 Externally sponsored research in developing countries raises ethical issues not only during research but also once the clinical trial or study is over. Researchers, sponsors and research ethics committees have to consider whether an intervention found to be efficacious in a completed trial should continue to be provided to the research participants, and to the local community. Many people would like to see participants given guaranteed access to interventions shown to be successful once the research is complete. However, subsequent access to successful interventions or the maintenance of an improved standard of healthcare to participants, and especially to the wider community, is rarely a simple matter. Providing access will depend upon several factors including the existence of alternatives, the relative burden of the disease, and the costs of supplying treatment. Expensive interventions that initially appear too costly to implement may become affordable within a short period of time.
- 4.2 Uncertainty about whether an experimental intervention will prove to be successful or locally affordable, and the difficulty of guaranteeing that it can be provided to participants in the longer term, have discouraged sponsors from making commitments of this nature before embarking on a trial. The possibility of introducing an intervention may depend on support from external bodies, other than those sponsoring the research, as well as action by national governments. How much effort should be made by sponsors to secure access in order to ensure that research is ethically acceptable is therefore difficult to judge. There is a growing consensus however, that the ethical review process, undertaken before the research starts, should address the issues that may arise when the trial or study is concluded. (See also NCOB 2002, Chapter 9.)
- 4.3 In the Workshop, three issues that arise once research is complete were considered:
- should post-trial treatment be provided?
 - who should supply treatment or provide interventions?
 - determining when research is over.

Should post-trial treatment be provided?

Guidance

- 4.4 In general, there is consensus in the guidance that participants should benefit from taking part in research¹ (Appendix A, Table 3). For example, WMA 2000 requires that:
- ‘At the conclusion of the study, every patient entered in the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods.’²
- However, recent discussion at the WMA about a proposed revision to this paragraph led to ‘sharp differences of opinion’. It was eventually agreed that the paragraph should not be amended but that a Note of clarification should be added (see Box 4.1).
- 4.5 WMA 2000 does not define in any detail how the requirement to assure access to treatment should be achieved. EGE 2003, however, specifies that ‘free supply of a proven beneficial new drug’ must be arranged for all the participants of a trial after the trial is ended, provided that

¹ WMA 2000, paragraph 30; CIOMS 2002, Guideline 10; EGE 2003, paragraph 2.13; NCOB 2002, paragraph 9.31; National Bioethics Advisory Commission (2001) *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries* (Bethesda: NBAC), Recommendation 4.1.

² WMA 2000, paragraph 30.

the intervention is not available 'through the normal health care system', and that this may involve 'supplying the drug for a lifetime if necessary'.³ EGE 2003 also states that the clinical trial should benefit the community that contributed to the development of the drug. This could be achieved by guaranteeing a supply of the drug at an affordable price for the community, or by strengthening expertise.

- 4.6 NCOB 2002 and CIOMS 2002 acknowledge that it may not be possible in all cases to ensure post-trial access. However, they recommend that possible options should be clarified before the trial begins.⁴ CIOMS 2002 notes in Guideline 10 that:

'Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that ... any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.'

The Commentary on Guideline 10 notes that 'for minor research studies and when the outcome is scientific knowledge rather than a commercial product, such complex planning or negotiation is rarely, if ever, needed.'

Workshop discussion

- 4.7 The main doubt expressed by delegates was that it was unlikely to be feasible for sponsors to guarantee provision of an effective intervention after a trial in all circumstances. This was particularly true if continued treatment for chronic disease was involved as costs could be high in the long term.
- 4.8 There was support for the principle of addressing questions concerning availability of treatment at the planning stage. Delegates acknowledged that this approach may be difficult because the price of a medicine cannot be predicted before a trial is completed. However, considering the issues before the trial starts is likely to be beneficial; negotiations during the study or after its completion could lead to undesirable tensions and delays in making interventions available. Some delegates were concerned that an unrealistic burden would be placed on researchers if they were expected to secure post-trial access for participants. Others cited instances where such advance negotiation had been successful. For example, during trials of ARTs in Uganda and Zimbabwe, the sponsors and pharmaceutical companies had made it clear they would not pay for ART once the trial was over. However, the local ethics committees took the view that the trial was, on balance, beneficial to participants, in part because they would receive ART for four years. The researchers had then been able to obtain written confirmation from the relevant Ministers of Health accepting responsibility for continuing care of trial participants, including the continuing provision of ART. It was agreed that it would have been unrealistic to expect more than a provisional guarantee for lifelong therapy.
- 4.9 It was suggested that options for the availability of post-trial treatment for the wider community should also be explored. The main purpose of conducting clinical trials was to evaluate interventions that may have application in populations, of which the participants in the trial were but a sample. However, the guidance offers little advice about wider provision, which would be especially relevant to vaccine trials. A number of questions need to be considered. If a vaccine was found to be effective, who should provide it to the community? How many people should be treated? For how long should the vaccine be supplied? What additional costs would be involved? And most importantly, who should be responsible for

³ EGE 2003, paragraph 2.13.

⁴ CIOMS 2002, Commentary on Guideline 10; NCOB 2002, paragraph 9.31.

meeting those costs? Delegates agreed that these questions should be addressed in advance.

- 4.10 However, delegates also noted that in making the intervention available to all participants in a study or the wider community, the possibility of long-term surveillance to assess the safety of a treatment may be excluded. There would no longer be a control group for comparison with participants who received the intervention, which may make it difficult to detect later adverse effects. NCOB 2002 observes that this issue is not confined to clinical trials in developing countries and recommends that judgements would have to be made on a case by case basis.⁵

Box 4.1: Revision of WMA Declaration of Helsinki paragraph 30

Paragraph 30 of WMA 2000 concerning the provision of treatment to research participants reads:

'At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.'

The WMA established a Workgroup to consider an amendment to paragraph 30 of WMA 2000 in October 2001. However, 'sharp differences of opinion' at the WMA General Assembly in September 2003, led to the amendment not being adopted.* Instead, another Workgroup was established to clarify the controversy. The Workgroup's Report outlined three options:

- not to revise paragraph 30, but to add preamble explaining that the Declaration is not a regulatory or legal device;
- to add a note of clarification setting out the intention of the paragraph; or
- not to make any changes and to issue a separate statement on equitable access to healthcare.†

The proposed revisions to paragraph 30 were discussed during the Workshop. The Council submitted a response to the Workgroup's Report which drew on this discussion and the Council's 2002 (NCOB 2002) Report.‡

In May 2004, the Workgroup announced its decision that paragraph 30 would not be amended and nor would a preamble be added. However, a Note of clarification was later added to the Declaration stating that:

'The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.'[§]

* World Medical Association (2003) Press release 14 Sept *WMA to continue discussion on Declaration of Helsinki*. Available: http://www.wma.net/e/press/2003_19.htm Accessed on 3 Feb 2005.

† World Medical Association (2004) *Workgroup Report on the revision of paragraph 30 of the Declaration of Helsinki*.

‡ Submission by the Nuffield Council on Bioethics to WMA. Available: www.nuffieldbioethics.org/developingcountries Accessed on: 3 Feb 2005.

§ World Medical Association (2004) Press release 11 Oct *Clarification on Declaration of Helsinki*. Available: http://www.wma.net/e/press/2004_24.htm Accessed on: 3 Feb 2005.

⁵ NCOB 2002, paragraphs 9.17–9.20.

Who should supply treatment or provide interventions?

Guidance

4.11 Most of the guidance does not address the question of where the responsibility of providing interventions after research is over should lie (Appendix A, Table 3). Neither WMA 2000 nor EGE 2003 comments on which organisation should supply treatment. However, CIOMS 2002 states that it is the sponsor who should provide post-trial access to treatment.⁶ In contrast, NCOB 2002 concluded that the provision of new medicines or improved healthcare was primarily the responsibility of national governments, and that sponsors of research were not in a position to make unilateral decisions at the start of a trial without appropriate consultation.⁷

Workshop discussion

4.12 Delegates acknowledged that decisions about post-trial treatment involved several different stakeholders, and that it was important to recognise the complex interplay between them. They included sponsors (both public and private), local governments, policy makers, researchers and physicians. There was some debate as to whether it was either useful or realistic to consider these stakeholders as members of a 'team' but it was suggested that, in any event, it was important to establish an early dialogue between these different groups (see Box 4.2). It was suggested that continued discussion might help to establish a transparent and efficient mechanism for providing post-trial treatment, and by defining shared responsibilities, it would be possible to ensure sustainability and independence.

Box 4.2: Providing the intervention after the trial is over – ARTs in Brazil (case study contributed by Professor Carlos Brites)

In Brazil, a Resolution advises that 'Access to the medicine being tested must be assured by the sponsor or by the institution, researcher, or promoter, if there is no sponsor, in the event its superiority to the conventional treatment is proven'.*

Researchers designing a trial for ARTs to treat HIV/AIDS patients, initially faced resistance to this requirement, because of the high price of the medicines. However, after negotiation, all companies involved in sponsoring the trial agreed to comply. In one particular trial investigating the medicine Enfuvirtide (T-20), a pharmaceutical company provided supplies for more than two years after the trial was completed, without cost to the participants. The Brazilian Ministry of Health is currently negotiating with the company to buy T-20 for the public health system. It is expected that patients will continue to receive the medicine in the same way but the provider will be the government rather than the company.

* Resolution 251 (251/97/IV.1.m) Brazilian National Health Council.

4.13 The roles of particular stakeholders that were discussed included:

■ Sponsors:

Delegates recognised that if researchers or sponsors were categorically required to fund the future provision of interventions, either to participants in the study or to the wider community, many would be likely to cease supporting research. In particular, sponsors from the public sector are unlikely to be able to bear the costs involved without curtailing other research.

⁶ CIOMS 2002, Guideline 10.

⁷ NCOB 2002, paragraph 9.36.

■ *Physicians:*

One of the suggested revisions for paragraph 30 of WMA 2000, which was under consideration at the time of the Workshop by a WMA sub-committee (see Box 4.1), stated that physicians 'should make every effort to ensure that all patients... will have access to any ... therapeutic method'.⁸ However, delegates observed that this wording was problematic. Although the primary support should come from physicians, they would seldom be in a position to guarantee availability of treatment. The role of other stakeholders needed to be acknowledged. In addition, it may be more realistic to suggest that those involved should make 'appropriate efforts' rather than 'every effort'.

■ *National government:*

It was suggested that it was important to assess the capacity of national health care systems to introduce and sustain interventions. Research should be aligned with, and aim to strengthen, existing national health programmes. Researchers and sponsors should be proactive in liaising with relevant government departments to ensure the availability of treatment after a trial. Involving the community at an early stage should also help to develop long-term solutions that are feasible and realistic so that services can be maintained after the study is completed (see also Box 3.5). It was observed that further analysis, and consideration of other factors such as national priorities, cost-effectiveness and other research findings, would often be necessary to determine whether an intervention should be implemented. Such evaluation should be the responsibility of policy makers.

When is research over?

Guidance

- 4.14 The question of how to determine when a study, trial or research project is complete is not addressed in the guidance. However, delegates considered a proposed revision of paragraph 30 of WMA 2000, which, had it been approved by the WMA General Assembly, would have required a new intervention to be made available 'once it has been approved by the appropriate authorities'.⁹

Workshop discussion

- 4.15 Delegates agreed that it is not always a straightforward matter to determine when research is complete. Not all research leads directly to useful interventions that can be introduced into routine care. The requirement that treatment should be made available after all clinical trials is, therefore, not meaningful, and delegates suggested that the issue should be clarified in the guidance. Examples of research that would not necessarily result in a treatment being made available included:

- Phase I trials that do not immediately result in proven treatment (see Box 4.3).
- Single research studies: these rarely lead to the discovery of a new intervention that can be introduced immediately into routine care. Operational research to define how a new intervention may be integrated into the healthcare system and the feasibility of its introduction need to be addressed before access can be agreed.

⁸ World Medical Association (2003) Workgroup Report on the revision of paragraph 30 of the declaration of Helsinki, paragraph 3.1. and 3.2. Available: http://www.wma.net/e/pdf/wg_doh_sept2003.pdf Accessed on: 3 Feb 2005.

⁹ World Medical Association (2003) Workgroup Report on the revision of paragraph 30 of the declaration of Helsinki, paragraph 3.2. Available: http://www.wma.net/e/pdf/wg_doh_sept2003.pdf Accessed on: 3 Feb 2005. See also World Medical Association (2004) Press release 11 Oct *Clarification on Declaration of Helsinki*. Available: http://www.wma.net/e/press/2004_24.htm Accessed on: 3 Feb 2005.

- Epidemiological and observational studies, which do not usually translate into new medical interventions.¹⁰

Box 4.3: No immediate implementation of treatment – clinical trials of antimalarial treatments (case study contributed by Professor Malcolm Molyneux)

A research project was conducted in Blantyre, Malawi, to determine whether artesunate suppositories could provide initial beneficial therapy for children with severe malaria (see Box 2.2). A number of practical issues arose during discussion about the availability of treatment after the completion of the trial. It would not be possible to implement the treatment immediately and, in addition, it was not envisaged that the intervention would be provided to the trial participants themselves because:

- The trial participants were not the eventual target group of the research. The trial involved children with 'moderately severe' malaria, whereas the final therapy was intended for children with severe life-threatening malaria.
- The project involved an immediate short-term treatment for an acute disease. Participants in the trial would not require continuous therapy, although they may experience possible future episodes of the disease.
- The trial was an early efficacy study. Introduction of the treatment would require subsequent effectiveness studies. It would also be necessary to establish additional facilities to deliver the intervention before it could be made widely available.

See Barnes KI, Mwenechanya J, Tembo M, McIlleron H, Folb PI, Ribeiro I, Little F, Gomes M, Molyneux ME (2004) Efficacy of rectal artesunate compared with parenteral quinine in initial treatment of moderately severe malaria in African children and adults: a randomised study *Lancet* **363**:1598-605.

- 4.16 Researchers, sponsors and local health authorities may differ in their view of how successful a trial has been. Questions were raised about how effective an intervention must be shown to be before it merits provision. For example, if a vaccine is shown to give a 50% protection, should it be widely introduced?
- 4.17 Delegates noted that guidelines requiring a new intervention to be made available 'once it has been approved by the appropriate authorities'¹¹ may not always be practical for two reasons:
- There may be a risk that suspending the provision of treatment until regulatory approval will leave trial participants without treatment. This would be especially relevant in the case of trials of interventions to control potentially fatal chronic conditions.
 - It could also lead to delay in the provision of treatment to the wider community. If trials of interventions are sufficiently advanced, the question of access could be explored before full regulatory approval. This is especially important in the case of interventions regarding life-threatening or seriously debilitating conditions where alternative interventions are ineffective or unavailable.

Summary of discussion about what happens once research is over

- 4.18 Wherever possible, the results of trials where interventions prove to be effective must be translated to improve healthcare for communities in which they were undertaken. It was

¹⁰ See also NCOB 2002, paragraph 9.34.

¹¹ Under consideration at the time of the Workshop by a WMA sub-committee established to review paragraph 30 of WMA 2000, see World Medical Association (2003) Workgroup Report on the revision of paragraph 30 of the declaration of Helsinki, paragraph 3.2. Available: http://www.wma.net/e/pdf/wg_doh_sept2003.pdf Accessed on: 3 Feb 2005. See also Box 4.1.

agreed, therefore, that discussions about what should happen once research is over are particularly crucial. However, most of the guidance does not address the practicalities of the provision of interventions, or where the responsibility should lie.

4.19 Several themes emerged throughout the Workshop. These were:

- It is essential to begin negotiations about post-trial treatment at an early stage when planning research. This reaffirms the recommendations of CIOMS 2002 and NCOB 2002, and the recent Note of clarification added to WMA 2000, which states that it is necessary to identify post-trial access 'during the study planning process'.
- Early discussions should be held between a range of different stakeholders, including sponsors, researchers and physicians, health authorities and governments. However, there is no agreed mechanism for such negotiations.
- Governments need to assess the capacity of national health programmes and consider issues of the consequences of providing new interventions when allocating resources. For example, if a hepatitis B vaccine were introduced into an infant vaccination programme, would this prevent the provision of other interventions as a result of limited resources?
- It is unlikely to be feasible in practice to guarantee provision of an effective intervention after a trial in all circumstances. Guidance that requires researchers or sponsors to fund the provision of interventions once the research is complete may be unrealistic and lead to sponsors curtailing other research.
- It is not always a straightforward matter to determine when research is complete, and some of the requirements in the guidance to provide post-trial access might not always be feasible.
- Research has the potential to provide benefits to a community that are not confined to the provisions of the particular study and these may be more enduring than the provision of the tested intervention. These benefits may include:
 - increasing the number of people able to contribute professionally to healthcare;
 - assisting the development of the skills and expertise of local scientists;
 - improving health infrastructure; and
 - increasing the potential for a sustained improvement in healthcare services (see also paragraphs 6.7–6.8).
- Attention should be given to these potential improvements during discussion about the post-trial availability of treatment to both research participants and the wider community.

Chapter

Ethical review

5



Ethical review

Introduction

- 5.1 An effective system for ethical review of research provides a crucial safeguard for research participants. While this process is typically undertaken by independent Research Ethics Committees (RECs), there are still many countries in the developing world in which these bodies are absent, ineffective or under-resourced. In addition, there may not be a pool of sufficiently trained and independent people to serve on such committees. As we have said, the inequalities in resources that exist between developed and developing countries pose significant risks of exploitation when externally sponsored research is carried out. The structure of RECs, the scope of their work and the mode of their operations are therefore particularly important in the context of research in developing countries.
- 5.2 A critical issue is whether there should be separate scientific and ethical review, and whether review should take place in both the sponsor's country and the country in which research is to be conducted (the host country). The independence of RECs is crucial and their sources of funding need thorough consideration. The scope of the responsibilities of RECs also needs to be carefully defined, including their role after a trial has begun, addressing conflicts when more than one ethics committee is involved, and ensuring adequate training for committee members in order to build capacity, skills and experience (see also NCOB, Chapter 8).
- 5.3 In the Workshop, the following issues were discussed:
- should there be separate scientific and ethical review of research?
 - where should review take place?
 - what kind of funding and support is appropriate for a REC in the host country? and
 - what is the role of a REC after the approval of research?

Should there be separate scientific and ethical review of research?

Guidance

- 5.4 The guidance generally agrees that ethical review of research should take place and that it should be conducted by at least one independent REC¹ (Appendix A, Table 4). However there are different views regarding the need for separate scientific and ethical review, and whether or not it is appropriate for a REC to review the scientific validity of a study.
- 5.5 NCOB 2002 recommends that scientific and ethical review should, where possible, be undertaken separately because they have different purposes. This may, but will not necessarily, require the establishment of two committees.² In contrast, WMA 2000, CIOMS 2002 and EGE 2003 do not require a separate committee for scientific review.³ CoE 2004 requires independent examination of the scientific merit of a proposal, followed by ethical review and approval by a 'competent body'.⁴

¹ WMA 2000, paragraph 13; CIOMS 2002, Guidelines 2 and 3; CoE 2004, Articles 9 and 10; EU 2001, Articles 3, 6 and 9; EGE 2003, paragraph 2.8; NCOB 2002, paragraph 8.2.

² NCOB 2002, paragraphs 8.4 and 8.5.

³ WMA 2000, paragraph 13; CIOMS 2002, Commentary on Guidelines 2 and 3; and EGE 2003, paragraph 2.8. All agree that ethical and scientific review must take place.

⁴ CoE 2004, Article 7 states: 'Research may only be undertaken if the research project has been approved by the competent body after independent examination of its scientific merit, including assessment of the importance of the aim of research, and multidisciplinary review of its ethical acceptability.' The phrase 'competent body' is used to indicate that in some countries the ethics committee may be the competent body, whereas in others the competent body might be a Ministry or a regulatory agency that would take the opinion of the ethics committee into account, see Explanatory Report, paragraph 28. See also Article 9: *Independent examination by an ethics committee*.

Workshop discussion

5.6 During discussion, there was broad agreement that both the scientific quality, and the ethical issues raised by the proposed research should be reviewed but there was disagreement as to how this should be achieved. Ideally, and where feasible, it was suggested that these review processes should be separated (see also Box 5.1). In Kenya, for example, a scientific committee usually reviews the scientific protocol before it is submitted to an ethics committee. If the scientific committee does not have enough expertise, an external Kenyan expert is sought to review the protocol. In a much smaller country such as Fiji, there are not currently enough suitably qualified experts to make it possible to create two separate committees. One suggestion was that it might be more appropriate to specify that a REC has a duty to ensure that there is adequate review of both the ethical and the scientific aspects of a proposal, rather than stating how this should be achieved.

Box 5.1: Ethical review in a host country – South Africa (case study contributed by Professor Ames Dhali)

In South Africa, the National Health Act No. 61 (2003) makes it a legal requirement that any research related to healthcare must have approval from a REC registered with the National Health Research Ethics Council. The Council, appointed by the Minister, is responsible for registering and auditing RECs.

There are currently more than 20 RECs in the country, including Provincial Research and Ethics Committees, RECs in tertiary institutions and private RECs. The Department of Health's Clinical Trials Guidelines (2000) recommend that a REC should include members who have the qualifications and experience to review and evaluate the scientific, clinical, and ethical aspects of the proposed trial.* Most RECs in the country are, therefore, able to conduct both scientific and ethical review, although the processes are often separated. They include:

- Institutional RECs (for example, eight are attached to medical schools): scientists on the committee who have appropriate expertise review the scientific aspects as part of the appraisal of the ethical issues. A separate scientific committee in the institution will also conduct an independent scientific review of undergraduate and postgraduate research projects. The same members may serve on both committees.
- MRC of South Africa Ethics Committee: a scientific review must have been conducted before a project is submitted to the Committee. However, there is also scientific expertise on the Ethics Committee itself.
- Committees of pharmaceutical companies: a pharmaceutical company will usually have an internal scientific committee to review a proposal when sponsoring clinical trials. The local REC will also examine both the scientific and ethical aspects of the proposal.

* South Africa Department of Health (2000) *Guidelines for good practice in the conduct of clinical trials in human participants in South Africa*, Guideline 8.2. Available: <http://www.doh.gov.za/docs/policy/trials/trials-full.html> Accessed on: 4 Feb 2005.

5.7 Delegates also discussed the development of regional committees for scientific and ethical review. A number of independently established regional fora for RECs have been established such as the Pan-African Bioethics Initiative (PABIN) under the auspices of the Strategic Initiative for Developing Capacity in Ethical Review (SIDCER). These committees assist with the development of expertise for ethical review, facilitate education and provide technical support. It was suggested that they might also have a useful role where a particularly difficult case is being reviewed, or one that raises new issues. However, such committees need direct

funding for their establishment and continued maintenance, and may not be able to expand their roles accordingly.

Where should review take place?

Guidance

- 5.8 One of the main points of disagreement in the guidance concerns the degree of involvement of the host country in the review process (Appendix A, Table 4). Three documents recommend that ethical review is undertaken in the host country. For example, CoE 2004 requires that an ethical review by an independent ethics committee be performed 'in each State in which any research activity is to take place'.⁵ NCOB 2002 recommends that research should be reviewed in both the sponsoring country(ies) and the host country(ies) in which research takes place.⁶ EU 2001 states that an opinion on the ethics of the proposed research should be given by each Member State participating in the trial.⁷
- 5.9 Other guidelines are less stringent. CIOMS 2002 does not necessarily require host countries to have a distinct fully functioning REC, although representatives from the host countries should be involved in the ethical review process.⁸ Similarly, EGE 2003 allows the review to be conducted by a mixed committee, with representatives from both EU Member States and host countries.⁹ WMA 2000 is the only guidance that does not address the need to have a REC in the host country.

Workshop discussion

- 5.10 During discussion, it was observed that proposals for externally sponsored research often have to be submitted to multiple reviews in both the host and sponsor country. A proposal may be reviewed by the REC at the local institution, the REC of the host country, the RECs of collaborators in the sponsor country, internal committees of the sponsors, and by any institutions where laboratory samples are analysed. Concerns were expressed that multiple review can cause long delays and a number of examples were cited. For example, for a study in Malawi, it took one and a half years for a protocol for a vaccine trial to be reviewed. Similarly, in a partnership to conduct a clinical trial of a rotavirus vaccine in India, it took nine months for a protocol to be reviewed by four different RECs. Each REC has a different schedule of meetings. Passing a proposal sequentially between the four committees can take several months. If one REC makes alterations to a proposal, the others will often want sight of the revised version, causing further delays. However, if researchers send their proposal to several committees simultaneously, and the different committees request different revisions, re-circulation of the new draft between all parties can also cause delays (see also Box 5.2).
- 5.11 If the review process is to achieve its aim of improving the quality of research, the process needs to be made more efficient. One possibility, discussed during the Breakout Groups, would be to improve mechanisms for communication between different RECs reviewing the same protocol. Methods discussed included: encouraging the exchange of information between committees; copying all correspondence to the other RECs as well as to the investigator; and facilitating visits between committees of the host and sponsor countries.

⁵ CoE 2004, Article 9. Article 29 also considers the possibility that research might take place in a country that is not party to this Protocol, or in a country where no suitable body for the review of research exists, see Appendix A, Table 4.

⁶ NCOB 2002, paragraph 8.22.

⁷ EU 2001, Articles 3.2a and 9.

⁸ CIOMS 2002, Commentary on Guideline 3.

⁹ EGE 2003, paragraph 2.8.

Improving the channels of communication would help reduce tensions and conflicts between committees, develop consistency of decisions and also enable better understanding about the local context in which the research is to take place.

- 5.12 It was suggested that in some circumstances, the responsibilities between committees could be devolved, with individual RECs reviewing only parts of a proposal. This idea accords with CIOMS 2002. These guidelines suggest that RECs in the sponsor country have a specific responsibility to review the scientific methods, whereas committees in the host country should determine whether the objectives of the research are responsive to the health needs of that country, review the detailed plans for compliance, and assess the ethical acceptability of the research proposal in light of the local community's customs and traditions.¹⁰ (See also paragraph 6.23 for further discussion of the role of a REC in assessing the research priorities of a country.)
- 5.13 For some issues, it was considered essential to include local expertise in the review process. The host REC, with knowledge of the local and cultural context, may be better placed to comment on issues concerning research priorities, consent, inducements and the protection of research participants. However, as discussed earlier (see paragraphs 2.14–2.16 on consent), innovative methods may be required to ensure adequate lay representation (see also Box 6.1). Many RECs already included lay members, but the importance of ensuring that they could contribute effectively needed to be emphasised.
- 5.14 Another issue concerned the primacy of the host and sponsor committees. In general, it was considered more important to have dialogue rather than dominance between different committees, although there was a need to recognise that committees may differ in their expertise. However, delegates suggested that in most situations the local host committee should be able to make the final decision. In practice, however, it was considered unlikely that a sponsor would be willing to fund a project where either the host REC or the sponsor country's REC had not given approval. Some sponsors require a proposal to have received local REC approval before it is submitted for funding. Such a requirement may prove burdensome for a local committee. If a grant is then not approved, an already under-resourced REC will have wasted both time and effort.
- 5.15 Some delegates suggested that a substantial expansion in the number of externally sponsored clinical trials in developing countries was likely to occur over the next decade. Greater investment in research by private foundations, and the pharmaceutical industry, and new initiatives such as the European and Developing Countries Clinical Trials Partnership (EDCTP) could be expected to increase pressure on local ethics committees. Under these circumstances, more effective committees that can function well at the local level would be essential.

¹⁰ CIOMS 2002, Commentary on Guideline 3.

Box 5.2: Ethical review in a host country – Brazil (case study contributed by Professor Carlos Brites)

The National Ethics of Research Committee (CONEP) was established by the Brazilian National Health Council (CNS) in 1996 (Resolution 196/96). CONEP is responsible for the evaluation of all research involving humans, particularly projects involving genetics, human reproduction, indigenous populations, biosafety issues, research supported by foreign countries or institutions, or involving the export of biological materials. CONEP reviews projects after approval has been given by the local REC. It also has a regulatory and advisory role, and manages disagreements between local RECs and researchers.

After a period of adaptation, the system is now considered to be operating well and conflicts between CONEP and investigators are rare. However, there are still concerns about the time taken to resolve issues raised by specific projects. Because a project must be approved at two different levels, it usually takes three to four months for final approval to be received.

What kind of funding and support is appropriate for a REC in the host country?**Guidance**

5.16 The guidance agrees that ethical review of research should be conducted by a REC independent of undue financial or political influence¹¹ (Appendix A, Table 4). However, there is conflicting advice as to the type of support or funding that may be appropriate to enable a REC to function effectively. EGE 2003 states that EU Member States may provide funds directly for capacity building and maintenance of RECs in host countries. CIOMS 2002 considers that sponsoring countries have a responsibility to support the development of capacity of RECs in developing countries, but does not state whether this contribution should be provided to the host country directly or indirectly.¹² In contrast, NCOB 2002 suggests that it is the responsibility of national governments to ensure the functioning of a REC, and recommends that committees should be funded indirectly to prevent problems of bias.

Workshop discussion

5.17 A number of delegates described difficulties faced by RECs in their own countries (see Box 5.3). The situations described reflected problems experienced in several countries, including for example, Peru. It was suggested that direct financial support by the sponsor to the REC may not be the best solution. Instead, funds could be put into a central pool for allocation to individual RECs. However, there were concerns that some institutions did not honour their commitment to support RECs. In the case of collaborative research, for example, a substantial proportion of the funding that was sometimes allocated to the institution for indirect costs often failed to be translated into funding for REC activities.

5.18 A number of different ways in which sponsors could assist the development of RECs in host countries were considered. These included the provision of training, general resources such

¹¹ WMA 2000, paragraph 13; CIOMS 2002, Guideline 2; CoE 2004, Article 10; EU 2001, Article 9; EGE 2003, paragraph 2.9; NCOB 2002, paragraph 8.20.

¹² CIOMS 2002, Commentary on Guideline 20: 'External sponsors and investigators have an ethical obligation to contribute to a host country's sustainable capacity for independent scientific and ethical review and biomedical research.' However, Guideline 2 states that: 'sponsors of research and institutions in which the investigators are employed should allocate sufficient resources to the review process. Ethical review committees may receive money for the activity of reviewing protocols but under no circumstances may payment be offered or accepted for a review committee's approval or clearance of a protocol.' This suggests direct funding may be acceptable. NBAC guidelines also agree that 'US sponsors and researchers should assist in building capacity of ethics review committees in developing countries'. See National Bioethics Advisory Commission (2001) *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries* (Bethesda: NBAC), Recommendation 5.7.

as IT and communications equipment, and providing a direct fee for specific services. It was noted that if a committee introduced a charge for reviewing a project to cover the costs, the charge should apply regardless of whether or not the project was approved. In some countries, the fee had sometimes only been charged if a project was approved.

- 5.19 The importance of providing training for members of RECs was also emphasised. Sponsors could contribute by providing training to members of committees to enhance the skills and understanding of the ethical review process. Initiatives to develop capacity for ethical review were seen to be particularly valuable and sponsors could play an important role in encouraging such programmes. For example, the Wellcome Trust sponsors training opportunities for members of ethics committees in developing countries through its Biomedical Ethics Programme.¹³ Delegates pointed out that an adequate infrastructure was crucial to ensure that knowledge acquired could be put into practice.

Box 5.3: Difficulties faced by local RECs – Kenya (case study contributed by Dr Job Bwayo)

In Kenya, members of the REC are expected to offer their services voluntarily, although a small amount of money may be available to compensate for time and travel expenses. Almost all of the members have been trained according to good clinical practice guidelines issued by ICH (see paragraph 1.12). They also receive annual training funded by foreign sponsors. However, the rapid turnover of trained staff makes it very difficult to sustain continuity.

Most members are not directly involved in research and find the review of large numbers of research protocols burdensome. The REC has limited office space in a hospital and a university, with no facilities for communication, photocopying or for keeping records. Although there are computers, there is no Internet connection and no access to a resource centre. This makes it difficult for members to perform literature searches or to familiarise themselves with specialised subjects under review.

An independent office for the REC with adequate administrative support is needed. However, this development would require significant additional funding. A small fee is charged for review of protocols but the funds received are retained by the institution and not used to support the REC. Current funding from the government, which is given to the institution rather than direct to the REC, is not adequate to sustain an independent REC.

- 5.20 Another means of providing additional funding for RECs could be for committees to charge for some of the functions that they perform, such as assessing research proposals at an early stage. It was also suggested that institutions could impose a charge for reviewing grant proposals to provide a source of internal funding to support the administration, and infrastructure required by a REC. However, care would need to be taken to avoid possible conflicts of interest.
- 5.21 A number of delegates asked about the availability of advice to guide those concerned with establishing RECs. It was noted that the WHO had produced guidelines giving general

¹³ The Wellcome Trust Ethics of Biomedical Research in Developing Countries grant schemes. Available: <http://www.wellcome.ac.uk/funding/medicalhumanities/biomedicalethics>. Other examples include initiatives funded by the Fogarty International Center (International Bioethics Education and Career Development Award, see <http://www.fic.nih.gov/programs/bioethics/bioethicsaward.html>); Harvard University (International Fellowship in Health Research Ethics, see <http://www.hsph.harvard.edu/bioethics>) and International Research Ethics Network for Southern Africa (IRENSA) (see <http://www.irensa.org>) (Accessed on: 4 Feb 2005).

standards of practice, including operating procedures and recruitment of members.¹⁴ This advice could provide a sound basis for initiating discussion and could be adapted to fit local circumstances. PABIN, SIDCER and the Council of Europe had also published some relevant literature (see Appendix D).

What is the role of a REC after the approval of research?

Guidance

5.22 Some elements of the guidance (WMA 2000, CIOMS 2002, EU 2001) suggest that RECs have an obligation to follow up research or to conduct monitoring.¹⁵ CIOMS 2002 for example states that:

'The ethical review committee should conduct further reviews as necessary in the course of the research, including monitoring of the progress of the study.'¹⁶

Workshop discussion

5.23 There were some concerns that requiring a REC to monitor a research study after it had begun would increase the already burdensome workload of RECs. In most cases additional resources for monitoring would not be available. Some RECs might be able to achieve passive monitoring. At the very least, where ethical approval was time-limited, a REC might ask for a report before granting renewed approval. In the Caribbean and Pakistan, for example, some RECs give approval for a project to be conducted for one year. The researcher is then asked to provide an annual report on the conduct of the study and to confirm that the protocol is unchanged in order for the approval to be renewed. However, the process had proved to be inefficient because of incomplete reporting and follow-up of non-responders. Furthermore, in many countries, reports from researchers are received by data and safety monitoring boards, which lack a clear mechanism for communication with RECs.

5.24 Several delegates commented that RECs were not always seen to be consistent in their decisions. In some cases, there was anecdotal evidence of researchers 'shopping around' until they found a committee that gave a favourable decision on a project. This practice raised questions about how RECs themselves were reviewed, and whether it was necessary to conduct a wider or more systematic audit of their work. Some delegates thought that this process would be helpful and could be used to evaluate whether there were conflicts of interest or particular complaints about the way a committee functioned. However, others felt that it would add an extra level of unnecessary bureaucracy for members of RECs and could lead to further delays. It was suggested that it might be useful to consider a mechanism for accreditation of RECs. Alternatively, the standards set out by WHO (paragraph 5.21) could be used as the basis for internal review. The RECs could also be audited by local regulatory authorities or international bodies.

Summary of discussion about ethical review

5.25 All agreed that the ethical review of research played a crucial role in protecting research participants. The fact that the process in the host and sponsor countries was beset by a number of problems, ranging from logistical delays to more substantive differences of opinion that could not be resolved by consultation with the guidance, was a major concern.

¹⁴ World Health Organization (2000) *Operational Guidelines for Ethics Committees That Review Biomedical Research* (Geneva: WHO).

¹⁵ WMA 2000, paragraph 13; CIOMS 2002, Guideline 2; EU 2001, Article 3.

¹⁶ CIOMS 2002, Guideline 2.

5.26 Several themes emerged throughout the Workshop:

- RECs have a duty to ensure adequate review of both ethical and scientific aspects of research proposals.
- In order to realise the benefits of ethical review, the process needs to be made much more efficient.
- Innovative methods of collaboration could be used to improve communication between different RECs, particularly between committees in the host and sponsor countries.
- Responsibilities might be devolved between committees. For some issues, the local expertise of the host REC is crucial.
- RECs in developing countries face serious difficulties through a lack of funding and a need to maintain independence.
- A particular problem is a lack of expertise among members of RECs. Initiatives to develop expertise in ethical review, through training and capacity building, are crucial.
- There were concerns that requiring a REC to monitor research after it had begun would increase the already burdensome workload of RECs.

Chapter

General themes

6



General themes

6.1 The issues raised by consent, standards of care, post-trial access to treatment, and ethical review in externally sponsored research are interrelated, and decisions reached in one of these four areas will often have a bearing on discussion about another. Clearly, all four areas need to be considered together in the design of a research proposal. During the Workshop discussion, some common themes were identified that cut across several aspects of research. In this chapter we discuss these general themes and examine the way that they are addressed in the guidance. The themes identified include:

- innovative ways of encouraging community participation in research;
- development of expertise;
- sustainability;
- partnership; and
- ensuring feedback from research.

We then turn to a number of related issues that were discussed briefly at the Workshop. These are not given much attention in the guidance (see Appendix A), but would merit further discussion and debate. They concern:

- increasing awareness of chronic diseases;
- research on public health; and
- intellectual property.

We then discuss national priorities for research, which are increasingly recognised as a critical determinant of whether research proposals should be supported. Finally, in the light of the experiences and evidence discussed during the Workshop, we consider the practical experience of implementation of guidance in healthcare-related research.

Innovative ways of encouraging community participation

6.2 The importance of involving the wider community in externally sponsored research is already explicitly addressed in general terms in some of the guidance.¹ Throughout the Workshop, delegates emphasised the need for community participation when conducting research in developing countries. However, it was acknowledged that defining a 'community' was rarely straightforward and researchers might sometimes not be aware of the diverse interests of different members of a given community. In addition, divisions within a community, or competing pressures could make it difficult to reach agreement about health issues.

6.3 Bearing these limitations in mind, engagement with the community was seen to have two main roles. First, involving the community helped researchers and sponsors to develop and maintain trust in a research project. Secondly, local consultation provided a means of adapting research designs for use in particular communities. For example, it had been noted that the establishment of Community Advisory Boards in the HapMap project (see Box 6.1) and educational initiatives

¹ For example, CIOMS 2002 acknowledges the importance of ethics review committees having a thorough understanding of a community's customs and traditions, and recommends that the committee should have either members or consultants with such an understanding (Commentary on Guideline 3); it also recommends that 'sponsors and investigators should develop culturally appropriate ways to communicate information' (Commentary on Guideline 4). CoE 2004 states that the existence of an independent ethics committee ensures that the interests and concerns of the community are represented (Explanatory Report, paragraph 41). Other guidance, such as the WMA 2000 and EGE 2003, does not address the issue.

in the KAVI vaccine trials in Kenya (see Box 2.5) had improved awareness of the research in local communities. In the case of the consent process, community involvement could facilitate the provision of information to participants (see paragraphs 2.14–2.15 and Box 2.5), and discourage inappropriate inducements. The role of the community was also highlighted in discussion about the provision of post-trial treatment and ethical review of research. There was agreement that, wherever possible, lay members should participate in the review process.²

Box 6.1: Engaging with the community – Community Advisory Boards in the HapMap project (case study contributed by Professor Charles Rotimi)

The International HapMap Project aims to determine common patterns of variation in DNA sequences in the human genome and to make this information freely available in the public domain (see also Box 2.6). An international consortium will collect DNA samples from populations in Africa, Asia and Europe.

The importance of genuine engagement with the community has been recognised at all stages of the project. In Nigeria, communities were given an opportunity to share their views through a range of individual interviews, focus groups and community meetings before the project began. A survey was also conducted to assess community attitudes, beliefs and experiences, and participants were invited to comment on the way in which samples would be collected.

In addition, a Community Advisory Board (CAB) was established in July 2003, to provide continuing community review and oversight of the project. There are nine members, and the Chair and other positions were selected by an open and democratic process. The Coriell Institute for Medical Research, the sample repository, will provide up to US\$1,000 per year to defray associated expenses, and the CAB will hold periodic meetings. The CAB will liaise with Coriell to check that future uses of the samples are consistent with the uses described in the consent documents. The CAB will also continue to monitor engagement with the community, and public consultation to ensure that initiatives do not cease when the collection of samples is completed.

US\$50,000 was allocated by the project to initiatives to encourage engagement with the community. Those involved considered that the process has raised the standard of research. However, questions were posed as to whether other studies would be able to afford a commitment of this nature.

See The International HapMap Consortium (2003) The International HapMap Project *Nature* 426: 789–96; The International HapMap Consortium (2004) Integrating ethics and science in the International HapMap Project *Nature Reviews Genetics* 5: 467–75.

Development of expertise

6.4 The importance of strengthening local expertise in research while conducting externally sponsored research was also highlighted throughout the Workshop. Guideline 20 of CIOMS 2002 states that sponsors and investigators have an obligation to contribute to national and local capacity in biomedical research³ (see Appendix A, Table 4). NCOB 2002 accords responsibility to sponsors by suggesting that they require the development of local expertise in research to be included as an integral component of research proposals.⁴ The guidance of the MRC of South Africa also explicitly emphasises the need for the development of

² CoE 2004 emphasises the importance of having lay members on an ethical review committee (Article 9).

³ 'In externally sponsored collaborative research, sponsors and investigators have an ethical obligation to ensure that biomedical research projects... contribute effectively to national and or local capacity to design and conduct biomedical research, and to provide scientific and ethical review and monitoring of such research.' CIOMS, 2002, Guideline 20.

⁴ NCOB 2002, paragraph 9.52.

infrastructure and research capacity to be addressed before research is completed.⁵

- 6.5 Delegates took the view that all externally sponsored research had the potential to provide opportunities to increase the number of qualified scientists and to improve the skills of professionals. For example, in Fiji, there was often interest from external researchers to conduct projects investigating human genetics in local populations. Many of these projects, such as the investigation of the genetic basis for colour blindness, were unlikely to have immediate relevance to the local population or nationally defined priorities. However, they received approval from the local REC on the condition that a local researcher was included in the study, and the sponsor contributed to the strengthening of expertise during the project (see also paragraph 6.21). Delegates emphasised that researchers in developing countries needed to be actively involved in planning research and not merely responsible for implementing protocols initiated by foreign partners.
- 6.6 Delegates concluded that both researchers and sponsors should share responsibilities for strengthening expertise, and that partnerships to assist efforts to develop regional and national capacity should be established wherever possible. Sponsors could also support training programmes. For example, substantial progress has been made in the past few years in strengthening expertise in research on malaria through the activities of the African Malaria Network Trust (AMANET), which has run workshops in Good Clinical Practice, data management and research ethics. The Fogarty International Center and the Wellcome Trust also support research and training with a series of grants and programmes. As mentioned previously, the development of expertise in ethical review is urgently required (see also paragraphs 5.17–5.21).⁶

Sustainability

- 6.7 The importance of longer term considerations, including the sustainability of local healthcare facilities strengthened through externally sponsored research, was also emphasised. Local improvements needed to be planned so that they were sustainable once research was complete. One example cited was the AIDS Support Organisation (TASO) clinic in Entebbe, Uganda, where trials of a pneumococcal vaccine were conducted. The research infrastructure was subsequently used for trials of anti-retroviral treatments and the research activities also had a beneficial effect on improving the standard of routine care at the clinic.
- 6.8 The need for sustainability of health-related improvements is recognised in CIOMS 2002, which advises that ‘the development of a health-care infrastructure should be facilitated at the onset so that it can be of use during and beyond the conduct of research’.⁷ NCOB 2002 also suggests that the sustainability of any changes introduced for the purposes of research should be considered. However, improvements are usually financed from research funds and are unlikely to be sustainable by this means once the research is completed. As the Report comments, ‘much ill-feeling may be generated and further research in the particular community compromised, if, at the end of the study, the researchers leave and the improvements to healthcare are not sustained’.⁸ Delegates acknowledged that, in practice, it was often not possible for an institution to maintain improvements in the longer term. However, other achievements in developing expertise, whether of personnel, of attitudes or of infrastructure, may contribute towards sustainability.

⁵ Medical Research Council of South Africa (2002) *Book 1 Guidelines on ethics for medical research: General principles* (SA MRC), paragraph 11.4.4i.

⁶ Recent training initiatives include the International Research Ethics Network for Southern Africa (IRENSA), which offers a programme to train students in international research ethics in order to support RECs.

⁷ CIOMS 2002, Commentary on Guideline 10.

⁸ NCOB 2002, paragraph 9.10.

Partnerships

- 6.9 NCOB 2002 stressed that the context for externally sponsored research is one of considerable inequalities of power and advantage between developing and developed countries.⁹ A fundamental moral principle identified in this regard is that the more powerful have a duty to refrain from exploiting the vulnerability of the weaker. Furthermore, in order to avoid erosion of the principle in practice and to avoid unfairness, it is important for the duty to be observed uniformly by all individuals and organisations.
- 6.10 A recurring theme at the Workshop, reflecting support for this approach, was the crucial importance of discussion between the stakeholders in research. As one delegate commented, 'the whole research endeavour should be created as a partnership'. Researchers, sponsors, participants, the local community and the local health authorities should work in partnership before research begins. They should consider the importance of the research questions, procedures for obtaining consent, the provision of an appropriate standard of care, and the sustainability of arrangements once research is complete. The crucial nature of partnership in the research setting is recognised in some of the guidance.¹⁰ NCOB 2002 considers that promoting genuine partnerships between researchers in developed and developing countries should help to strengthen expertise in research and maximise the opportunity for the transfer of knowledge and skills.¹¹

Ensuring feedback from research

- 6.11 The need to make research findings available after research has been completed is also encouraged by the guidance.¹² WMA 2000 and EGE 2003 both specify that negative as well as positive results should be included. Delegates emphasised the importance of making research results available to local health authorities so that decisions could be made about healthcare in the future. How such information is provided to the community will vary according to the circumstances. NCOB 2002 suggests that a public meeting may be an appropriate forum.¹³
- 6.12 Providing feedback to individual participants in research would also help to strengthen a sense of partnership. Delegates commented that failure on the part of researchers to do so is a frequent reason for reluctance to participate in any subsequent research. However, CoE 2004 also recognises that the wishes of a participant *not* to receive information should be recognised and that, where appropriate, results should also be provided within a framework of healthcare or counselling.

Increasing awareness of chronic disease

- 6.13 Delegates observed that discussions about research in developing countries are often overly influenced by issues arising from clinical trials and research to investigate infectious diseases.¹⁴ However, the burden of chronic non-communicable disease (NCD) in developing

⁹ NCOB 2002, paragraphs 2.32, 4.19 and 10.10.

¹⁰ EGE 2003, paragraph 2.4: 'The involvement of all partners, from the funding institutions to the host countries or communities, is essential at each phase of the research activities, from the definition of the programme and of the research priorities, to the follow-up after the end of the trials. The involvement of local scientists from the host country at the very early stage of the planning and implementation ... is crucial to develop a culture of collaboration. Their knowledge of local conditions and traditions is also necessary to identify local needs.'

¹¹ NCOB 2002, paragraph 10.50.

¹² WMA 2000, paragraph 27; CIOMS 2002, Items 34 in Appendix 1 Items to be included in a protocol ... for biomedical research involving human subjects; CoE 2004, Articles 26–28; EGE 2003, paragraph 2.14; NCOB 2002, paragraph 9.40.

¹³ NCOB 2002, paragraph 9.40.

¹⁴ CIOMS 2002 acknowledges that trials to test vaccines and medicinal drugs 'constitute a substantial part of all research involving human subjects' (Preamble).

countries is increasing and will require more research in the future. NCDs, including cancer, diabetes, cardiovascular disease, chronic respiratory disease, and mental health disorders, currently account for almost half the global burden of disease. Moreover, the majority of deaths, disability and morbidity resulting from NCDs take place in low- and middle-income countries.¹⁵

- 6.14 There was general agreement that the guidance needed to give greater attention to research involving chronic diseases requiring long-term treatment, including those with infectious aetiology, such as HIV/AIDS. The need for long-term provision of any treatment that might be available after a trial is over poses particularly difficult questions in some settings.

Research on public health

- 6.15 There was also debate at the Workshop about whether sufficient consideration has been given in the guidance to research concerned with public health. Here, the best interests of research participants have to be balanced against the best interests of the community as a whole. The guidance emphasises clinical research, with particular focus on trials of new medicines or vaccines. However, many different types of research related to healthcare in developing countries involve public health, such as epidemiology, surveillance studies, and operational research.
- 6.16 For example, in deciding whether to introduce a new vaccine into a public health programme, there will be a need to know not only whether the disease is prevented but also the level of protection which is provided. It may therefore be important to continue a research trial not only until a positive effect is established but until there is a good estimate of the level of protection. In these circumstances, those in the group who have not received the vaccine may be disadvantaged. However this approach can provide public health authorities with the information necessary to make the best decision on the future use of the vaccine for the community as a whole.
- 6.17 The ambiguity of the division between research and the practice of public health was reflected in discussion at the Workshop. For example, a distinction is often made between research and surveillance; surveillance activities are sometimes classified as not requiring ethical review as they are a component of public health practice. However, they often have a research component. The WHO/UNAIDS Surveillance Working Group has recently commissioned a Paper on ethical issues in second generation surveillance.¹⁶ Published in April 2004, it sets out a number of guidelines, although it does not reflect official policy of WHO or UNAIDS. This document recommends that all surveillance activities should be subject to a process of wide ranging consultation with the community and to ethical review. It recognises the particular difficulties that are associated with the HIV epidemic, when people thought to be at risk or who are in fact at risk may be subject to stigmatisation, discrimination and violence. The authors conclude that as a result, confidentiality has assumed critical importance in the conduct of surveillance. The obligation to disseminate data and the right of participants to access test results is also emphasised.
- 6.18 CIOMS, recognising the tensions and 'special features' of epidemiological research, published *International Guidelines for Ethical Review of Epidemiological Studies* in 1991

¹⁵ World Health Organization *Noncommunicable Diseases and Mental Health Cluster*. Available: http://www.who.int/noncommunicable_diseases/en Accessed on: 2 Feb 2005.

¹⁶ Fairchild AL and Bayer R (2004) *Ethical issues to be considered in second generation surveillance* commissioned by the WHO/UNAIDS Surveillance Working Group. Available: http://www.who.int/hiv/pub/epidemiology/sgs_ethical/en/ Accessed on 2 Feb 2005.

(Epidemiological Guidelines).¹⁷ They address issues of consent, recommending that individual consent should be obtained together with agreement of a community representative. However, they acknowledge that obtaining individual informed consent may not always be practical and some flexibility may be required. For example, in some community-based randomised trials, whole communities are categorised randomly as to whether or not they receive an intervention. Ethical review is also required for all epidemiological studies. The 1991 Epidemiological Guidelines state that, during the ethical review process, ‘there is a responsibility to ensure that the Declaration of Helsinki and CIOMS guidelines are taken into account in epidemiological studies’.

- 6.19 CIOMS 2002 addresses issues of confidentiality of data and use of biological samples, with specific mention of epidemiological studies. The commentary to Guideline 18 acknowledges that ‘it is usually impractical to obtain the informed consent of each identifiable patient [in epidemiological studies]; an ethical review committee may waive the requirement for informed consent ... provided that there are secure safeguards of confidentiality’. Issues concerning research related to public health are not specifically addressed in other guidance, much of which relates to clinical trials for medicinal products.¹⁸

Intellectual property

- 6.20 Large-scale studies in genetic epidemiology are being conducted in several different populations, including The Gambia, Ghana, Kenya, Malawi, Mali, and Vietnam. One aim is to examine the extent to which susceptibility to malaria is determined by genetic variation in the human immune system. Because there are a number of complex interacting factors, very large sample sizes are needed from a range of different populations.
- 6.21 This form of research raises questions about benefit sharing. One of the main issues in the debate on access to genetic resources in developing countries concerns the relationship between intellectual property protection and the ownership and rights pertaining to the resources on which the intellectual property right has been based. Only recently has the international community sought to recognise and protect genetic resources through international agreements such as the Convention on Biological Diversity.¹⁹ The principles of benefit sharing and equitable access to genetic resources are widely accepted but remain difficult to implement. For example, what should happen if a gene that offers some protection against malaria is discovered in one specific community but not others? If a product is developed based on this finding, should only members of the community in which the gene was discovered benefit, or should all communities who were involved in the research benefit equally, and if so, how should they benefit? Furthermore, there are various stakeholders involved in research including participants, health professionals, epidemiologists, geneticists, and companies, who may all have an interest. It was suggested that arrangements for possible benefits should be based on a partnership between sponsors and researchers both in the sponsor and local country. Further discussion of these issues was set aside as they were beyond the scope of the Workshop. However, they will clearly require attention in the future.

¹⁷ The 1991 Epidemiological Guidelines took into account the proposed draft of the CIOMS International Guidelines for Biomedical Research Involving Human Subjects, produced in 1982. These guidelines are currently under revision in order to ensure they complement the most recent revision, CIOMS 2002.

¹⁸ CoE 2004 covers the ‘full range of research activities in the health field involving interventions on human beings’, where ‘intervention’ includes a physical intervention and any other intervention in so far as it involves a risk to the psychological health of the person concerned (Article 2). The Explanatory Report suggests this should be taken to include questionnaires, interviews and observational research, and genetic epidemiology (paragraph 17).

¹⁹ Commission on Intellectual Property Rights (2002) *Integrating Intellectual Property Rights and Development Policy* (London: CIPR).

Setting research priorities

- 6.22 National resources for research in developing countries are generally very limited and setting priorities for healthcare-related research is therefore crucial. The more a country can determine its own priorities and conduct its own research, the easier it will be to ensure that research proposed by external sponsors is appropriate and relevant to its national health needs. Those elements of the guidance (WMA 2000, CIOMS 2002, EGE 2003 and NCOB 2002) that address the issue of setting research priorities generally agree that populations should benefit from research undertaken in their community.²⁰ EGE 2003 emphasises that research protocols should be relevant to national health priorities.²¹
- 6.23 With regard to the question of how this might be achieved, CIOMS 2002 states that the health authorities of the host country should ensure that the proposed research is responsive to the health needs and priorities of that country.²² It also considers that national or local ethical review committees 'have a special responsibility' in this area.²³ Delegates considered the role of the research ethics committee should be as a 'gate-keeper' rather than to set research priorities. However, they affirmed that developing countries should have a mechanism to set research priorities for healthcare, to enable, *inter alia*, effective collaboration with external sponsors.²⁴ NCOB 2002 recommends that all countries should set priorities for research into healthcare.²⁵
- 6.24 The Millennium Development Goals (MDGs), adopted by 189 nations in the United Nations Millennium Declaration in September 2000, have provided an additional source of priorities. Specific goals address the need to reduce child mortality, improve maternal health, and aim to halt and begin to reverse the incidence or spread of HIV/AIDS, malaria and other diseases. However, delegates observed that adhering only to the MDGs may divert scarce resources from other priorities which may be as, or even more important in specific settings. Setting priorities at a national level was therefore considered to be crucially important.
- 6.25 Once diseases have been identified as a national priority for research, what kind of programmes should be implemented? For example, if malaria is specified as a priority, what types of research would be acceptable? Should basic research, clinical research, vaccine trials, intervention studies and operational research all be given equal priority, or should some types of research be given more emphasis? These questions were beyond the scope of the Workshop but clearly need to be addressed in future discussions.

²⁰ NCOB 2002 states: 'research proposals submitted to those committees should include an explanation of how new proven interventions could be made available to some or all of the host country population and that investigators should justify to the relevant research ethics committees why the research should be carried out if this is not thought possible' (paragraph 9.49). Similar provisions can be found in CIOMS 2002, Guideline 10; EGE 2003, paragraph 2.13 and National Bioethics Advisory Commission (2001) *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries* (Bethesda: NBAC), Recommendation 4.3: 'Whenever possible, preceding the start of research, agreements should be negotiated by the relevant parties to make the effective intervention or other research benefits available to the host country after the study is completed.'

²¹ EGE 2003, paragraph 2.9.

²² CIOMS 2002, Guideline 3.

²³ CIOMS 2002, Commentary on Guideline 3.

²⁴ The Council for Health Research for Development (COHRED) has published guidance on priority setting, including *Essential National Health Research* (ENHR), an integrated strategy for organising and managing health research in different countries. The Global Forum for Health Research has also reviewed methodologies for priority setting and the most recent report (Global Forum for Health Research (2004) *The 10/90 Report on Health Research 2003-2004* (Geneva: GFHR) includes a detailed analysis of the various approaches to setting research priorities.

²⁵ NCOB 2002, paragraph 2.31.

Implementing guidance

- 6.26 A survey of researchers at the Workshop suggested that they refer primarily to national and institutional guidelines when designing research protocols.²⁶ However, there is a wide range of other guidance and researchers are often uncertain about which of these documents need to be considered. The degree to which standards demanded by documents such as WMA 2000 *must* be achieved, and the degree to which they might be regarded as aspirational is also not always clear.
- 6.27 Most of the guidance we have discussed in this Paper, with the exception of CoE 2004, does not have the force of law (see Table 1.1)²⁷. However, some of the documents still have very real implications for policy and practice of healthcare-related research, as a Resolution, Declaration or voluntary code of practice often carries significant weight and influences policy makers who devise binding legislation. The Declaration of Helsinki (WMA 2000), for example, is widely regarded as the pre-eminent ethical guidance on healthcare-related research.²⁸ Its provisions are referred to in regulations governing research involving human participants. For example the EU Directive 2001/83/EC *on the Community code relating to medicinal products for human use* refers to the Helsinki Declaration, stating 'All clinical trials shall be carried out in accordance with the ethical principles laid down in the current revision of the Declaration of Helsinki.'²⁹ Similarly, many organisations and companies sponsoring research will frequently only provide funding if researchers abide by the requirements set out in WMA 2000. Even though it is not a regulatory device, it has far more influence than a document that merely formulates aspirational ideals.
- 6.28 However, questions remain about the duties that the Declaration imposes on researchers, sponsors and others. Are its terms non-negotiable or is some flexibility implied by its status as a declaration that is not directly legally binding? On one view, its provisions might be seen to be immutable and demanding standards that must apply in all circumstances regardless of resources and welfare considerations. Indeed, these are effectively the terms in which the Declaration sets out its primacy:

'Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.'³⁰

On another view, the Declaration might be seen to be aspirational in its aims, setting out ideals that may not be attainable by all in all circumstances, but which are nevertheless crucial in setting standards. As one delegate put it:

"We are aware that we do not always achieve perfection, but the guidelines provide useful ideals for us to aim towards."

²⁶ The survey of the delegates' views was conducted by the Wellcome Trust in May 2004 as part of a consultation about the Trusts' draft Position Statement for Wellcome Trust funded research involving human participants in developing countries.

²⁷ The Protocol is only binding for those countries that have signed and ratified it, and are party to the 1997 Convention on Human Rights and Biomedicine.

²⁸ Taking into account the Nuremberg Code, the WMA, the international professional association of physicians, developed the Declaration of Helsinki to help prevent any abuse of trial participants. In the years that followed, as national governments and a wide range of other organisations developed legislation and codes of practice to protect human subjects in research, the Declaration was an obvious and appropriate starting point.

²⁹ EU Directive 2001/83/EC, Annex I part 4 (B).

³⁰ WMA 2000, paragraph 9.

In this regard it is noteworthy that the WMA Workgroup established to consider the revisions of paragraph 30, explored the option of adding the following preamble ‘... explaining that the Declaration is a set of ethical guidelines, not laws or regulations’:

‘As a statement of principles, the Declaration of Helsinki is intended to establish high ethical standards that guide physicians and other participants in medical research involving human subjects. These ethical principles provide the basis of moral reflection on the means and goals of research involving human subjects, distinct from national legal and regulatory requirements. Interpreting the provisions of the Declaration regarding the design, conduct or completion of the research requires careful balancing of all of the Declaration’s ethical principles. Differences in interpretation should be resolved by physicians and other participants involved in the research who are most familiar with all relevant factors, including the needs of research participants and of the host population.’³¹

In the event, the preamble was not adopted and a Note of clarification was added to paragraph 30 (see also Box 4.1).

- 6.29 Other guidelines that have followed WMA 2000 have sought to interpret its articles to provide clarification for researchers, sponsors and others. For example, the CIOMS 2002 Guidelines seek to explain and develop WMA 2000, particularly in the context of research in developing countries. Sponsors including the UK MRC, the Wellcome Trust and the National Institutes of Health (NIH) have prepared guidelines specifically for those conducting externally sponsored healthcare-related research.³² These various guidelines have made an important contribution to the protection of human participants in that they have not only developed the guidance as a whole, but have also encouraged debate and raised awareness of the issues raised by research. However, the variability of the guidance across a range of issues is likely to continue to place those wishing to conduct research in developing countries in a quandary.
- 6.30 Some principles set out in international guidance, such as the need for individual consent to participate in research, have been endorsed as universal, although community randomised trials may provide an exception (see paragraph 2.8). However, other provisions in WMA 2000, such as those dealing with the standard of care that researchers and sponsors should provide to the control group during research, have been viewed as being too narrowly construed, and CIOMS 2002, CoE 2004 and NCOB 2002 accept different provisions.³³ Some of the differences may be attributable to variations in the scope and legal status of the guidelines. Nevertheless, the lack of consistency between different elements of the guidance, particularly between CIOMS 2002 and WMA 2000, is regrettable, especially in the developing country context where the risk of exploitation of vulnerable populations is significant. Would a decision by physicians involved in a trial to forgo the obligation to provide treatment to participants after the trial is over, as specified by WMA 2000 and EGE 2003, and follow instead the more flexible approach advocated by CIOMS 2002 and NCOB 2002, leave the sponsor open to criticism?

³¹ World Medical Association (2004) *Workgroup Report on the revision of paragraph 30 of the Declaration of Helsinki*. Available: http://www.wma.net/e/ethicsunit/pdf/wg_doh_jan2004.pdf Accessed on: 3 Feb 2005.

³² Medical Research Council (2004) *MRC Ethics Guide: Research involving human participants in developing societies* (London: MRC); Wellcome Trust (2005) *Wellcome Trust Funded Research Involving People Living in Developing Countries* (London: Wellcome Trust); NIH (1997) *Guidelines for the conduct of research involving human subjects at the NIH* (5th Printing August 2004) (Washington, DC: NIH).

³³ CIOMS 2002, Introduction and Commentary to Guideline 11; CoE 2004, Explanatory Report, paragraph 120; NCOB 2002, paragraphs 7.29–7.30.

- 6.31 It was apparent at the Workshop that the complexity experienced by researchers in the field is inevitably not addressed in the guidance. Difficulties in formulating general guidance that will apply in all circumstances are unavoidable. However, critics argue that in the absence of consistency between different guidelines, researchers and sponsors can simply select those that best suit their purposes.
- 6.32 In such situations, the formulation of national guidance assumes particular importance. By developing its own national guidance, a developing country is able to take account of its particular needs and cultural context. In NCOB 2002, the Council recommended that developing countries should be encouraged 'to take account of existing international and national guidance and to create national guidance for its clear and unambiguous application'.³⁴ The availability of such guidance provides a basis for sponsors and researchers to design research that takes account of local circumstances. A rigorous and effective process of ethical review is also crucial to assess the appropriateness of the proposed research.
- 6.33 Much progress has been made over the past few years in the development of national and international guidance and the strengthening of capacity for ethical review in developing countries. However, researchers, sponsors and governments need to be clearer how guidance is to be understood, and how it is interpreted in practice. Differences or ambiguities between guidelines may lead to unnecessary delays or even inhibit much needed research. As one delegate commented:
- "Ethical and scientific uncertainties should not paralyse us but incite us to make more progress."*
- 6.34 It is important to learn from experience. The Workshop provided the opportunity to consider specific examples and this proved to be a worthwhile approach. It may become easier to justify a change in the way ethical principles are applied when there is clear evidence that the approach that was previously advocated had harmful, and perhaps unexpected, consequences. For this reason alone it can be very helpful to review the situation every few years, as this Paper has attempted to do. New evidence, or new ideas, may indicate the need for a change in approach.

³⁴ NCOB 2002, paragraph 5.28.

Appendices



Appendix A: Comparison of guidance on research related to healthcare in developing countries

Table 1: Guidance relating to consent

Guidance	Relevant sections	Text and notes
WMA 2000	Paragraph 22	<p><i>Provision of information:</i></p> <p>Participants ‘must be adequately informed about:</p> <ul style="list-style-type: none"> • the aims and methods of the study; • the sources of funding and possible conflicts of interest; • the institutional affiliations of the researcher; • the anticipated benefits and potential risks; • the discomfort it may entail; and • the right to abstain from taking part in the study, or to withdraw from it at any time without reprisal.’ [Paragraph 22] <p><i>Recording consent:</i></p> <p>Written consent is preferable but ‘non-written’ consent can be acceptable in some cases:</p> <p>‘After ensuring that the subject has understood the information, the physician should then obtain the subject’s freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.’ [Paragraph 22]</p> <p><i>Other points:</i></p> <p>Paragraph 23 addresses the process of obtaining consent ‘if the subject is in a dependent relationship with the physician or may consent under duress.’ Paragraphs 24–26 consider how consent should be obtained when potential participants are legally incompetent, physically or mentally incapable of giving consent or for children.</p>
CIOMS 2002	Guidelines 4 - 7	<p><i>Individual informed consent</i></p> <p>‘For all biomedical research involving humans the investigator must obtain the voluntary informed consent of the prospective subject or, in the case of an individual who is not capable of giving informed consent, the permission of a legally authorized representative in accordance with applicable law.’ [Guideline 4]</p>
		<p><i>Who should give consent?</i></p> <p>Community consent may be required but should never replace individual consent.</p> <p>‘In some cultures an investigator may enter a community to</p>

Continued

Table 1: Guidance relating to consent (*continued*)

Guidance	Relevant sections	Text and notes
CIOMS 2002	Guidelines 4 - 7	<p>conduct research or approach prospective subjects for their individual consent only after obtaining permission from a community leader, a council of elders, or another designated authority. Such customs must be respected. In no case, however, may the permission of a community leader or other authority substitute for individual informed consent.’ [Guideline 4, Commentary]</p> <p><i>Provision of information:</i></p> <p>‘Before requesting an individual’s consent to participate in research, the investigator must provide the following information, in language or another form of communication that the individual can understand’, then lists 26 items including aspects of the design of the trial (randomisation, double blinding); possible health risks for participants, and treatment options; issues relating to data protection; and questions of liability in the case of disability or death resulting from injury related to the research.’ [Guideline 5]</p> <p>The commentary on Guideline 4 also addresses the importance of the ‘process’ of obtaining consent.</p> <p><i>Recording consent:</i></p> <p>‘Consent may be indicated in a number of ways. The subject may imply consent by voluntary actions, express consent orally, or sign a consent form. As a general rule, the subject should sign a consent form, or, in the case of incompetence, a legal guardian or other duly authorized representative should do so.’ [Guideline 4, Commentary]</p> <p><i>Waiving consent:</i></p> <p>‘Waiver of informed consent is to be regarded as uncommon and exceptional, and must in all cases be approved by an ethical review committee.’ [Guideline 4]</p> <p>‘Investigators should never initiate research involving human subjects without obtaining each subject’s informed consent, unless they have received explicit approval to do so from an ethical review committee. However, when the research design involves no more than minimal risk and a requirement of individual informed consent would make the conduct of the research impracticable (for example, where the research involves only excerpting data from subjects’ records), the ethical review committee may waive some or all of the elements of informed consent. [Guideline 4, Commentary]</p>

Continued

Table 1: Guidance relating to consent (*continued*)

Guidance	Relevant sections	Text and notes
CIOMS 2002	Guidelines 4 - 7	<p><i>Inducements:</i></p> <p>'Subjects may be reimbursed for lost earnings, travel costs and other expenses incurred in taking part in a study; they may also receive free medical services. Subjects, particularly those who receive no direct benefit from research, may also be paid or otherwise compensated for inconvenience and time spent. The payments should not be so large, however, or the medical services so extensive as to induce prospective subjects to consent to participate in the research against their better judgment ('undue inducement'). All payments, reimbursements and medical services provided to research subjects must have been approved by an ethical review committee.' [Guideline 7]</p>
CoE 2004	Article 13, 14	<p><i>Who should give consent?</i></p> <p>Individual consent required:</p> <p>'No research on a person may be carried out... without the informed, free, express, specific and documented consent of the person.' [Article 14]</p> <p><i>Provision of information:</i></p> <p>Article 13 lists the information that should be addressed during the consent process:</p> <p>'Persons being asked to participate in a research project shall be given adequate information in a comprehensible form... [covering] the purpose, the overall plan and the possible risks and benefits of the research project:</p> <ul style="list-style-type: none"> i. of the nature, extent and duration of the procedures involved, in particular, details of any burden imposed by the research project; ii. of available preventive, diagnostic and therapeutic procedures; iii. of the arrangements for responding to adverse events or the concerns of research participants; iv. of arrangements to ensure respect for private life and ensure the confidentiality of personal data; v. of arrangements for access to information relevant to the participant arising from the research and to its overall results; vi. of the arrangements for fair compensation in the case of damage; vii. of any foreseen potential further uses, including commercial uses, of the research results, data or biological materials;

Continued

Table 1: Guidance relating to consent (*continued*)

Guidance	Relevant sections	Text and notes
CoE 2004	Article 13, 14	<p>viii. of the source of funding of the research project. ... and their right to refuse consent or to withdraw at any time without being subject to any form of discrimination.’ [Article 13]</p> <p>Methods of providing the information are also discussed in the Explanatory Report, paragraph 72.</p> <p><i>Recording consent:</i></p> <p>Consent must be documented. ‘Express consent may be either verbal or written as long as it is documented. Best practice demands that written consent be obtained, except in exceptional circumstances.’ [Explanatory Report, paragraph 79]</p> <p><i>Inducements:</i></p> <p>Details of all payments and rewards to be made in the context of the research project must be considered by the ethics committee. [Appendix: Information to be given to the ethics committee]</p> <p><i>Other points:</i></p> <p>Article 15 discusses protection of persons not able to consent to research; Article 19 discusses research in emergency clinical situations, when a person is not in a state to give consent.</p>
EU 2001	Article 3.2	<p><i>Who should give consent?</i></p> <p>Individual consent is required: ‘A clinical trial may be undertaken only if: ...(d) the trial subject or, when the person is not able to give informed consent, his legal representative has given his written consent after being informed of the nature, significance, implications and risks of the clinical trial.’ [Article 3.2 d]</p> <p><i>Provision of information:</i></p> <p>‘A clinical trial may be undertaken only if, in particular: the trial subject or, when the person is not able to give informed consent, his legal representative has had the opportunity, in a prior interview with the investigator or a member of the investigating team, to understand the objectives, risks and inconveniences of the trial, and the conditions under which it is to be conducted and has also been informed of his right to withdraw from the trial at any time.’ [Article 3.2 b]</p>

Continued

Table 1: Guidance relating to consent (*continued*)

Guidance	Relevant sections	Text and notes
EU 2001	Article 3.2	<p>Recording consent:</p> <p>Verbal consent may only be obtained if the participant is illiterate: '...if the individual is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation.' [Article 3.2 d]</p> <p>Other points:</p> <p>Opening paragraphs (3) and (4) discuss the involvement of persons incapable of giving legal consent in clinical trials. Article 4 discusses consent for research involving minors, and Article 5 discusses trials on incapacitated adults not able to give informed legal consent.</p>
EGE 2003	Paragraph 2.7	<p>Who should give consent?</p> <p>Consent of family or community leader may be required in addition to individual consent:</p> <p>'The involvement of people with knowledge of the local conditions and traditions and able to defend the interest of those affected by the project is necessary to guarantee the most appropriate procedures of informing of the potential participants in a clinical trial. According to the local situation, it may be appropriate to seek agreement on the implementation of a research project from persons representative of or invested with a certain authority within the community, or the family. However, free and informed consent always has to be given by each individual involved in a trial.' [Paragraph 2.7]</p> <p>Recording consent:</p> <p>Does not indicate how consent should be best recorded.</p>
NCOB 2002	Chapter 6	<p>Who should give consent?</p> <p>Consent of senior family member or community leader may be required in addition to individual consent:</p> <p>'We recommend that, in circumstances where consent to research is required, genuine consent to participate in research must be obtained from each participant. In some cultural contexts it may be appropriate to obtain agreement from the community or assent from a senior family member before a prospective participant is approached. If a prospective participant does not wish to take part in research this must be respected.' [Paragraph 6.22, and discussion 6.18-6.22]</p>

Continued

Table 1: Guidance relating to consent (*continued*)

Guidance	Relevant sections	Text and notes
NCOB 2002	Chapter 6	<p><i>Provision of information:</i></p> <p>‘Information sheets and consent forms must be designed to assist participants to make informed choices. We recommend that the information provided should be accurate, concise, clear, simple, specific to the proposed research and appropriate for the social and cultural context in which it is being given.’ [Paragraph 6.40, and discussion 6.4–6.17]</p> <p><i>Recording consent:</i></p> <p>Verbal consent is acceptable only if written consent is inappropriate: ‘Where it is inappropriate for consent to be recorded in writing, genuine consent must be obtained verbally. The process of obtaining consent and the accompanying documentation must be approved by a research ethics committee and, where only verbal consent to research is contemplated, include consideration of an appropriate process for witnessing the consent.’ [Paragraphs 6.37-6.40]</p> <p><i>Inducements:</i></p> <p>‘We recommend that dialogue is needed with sponsors, external and local researchers and communities to ensure that any inducements to take part in research are appropriate to the local context, especially in circumstances where the research exposes participants to a risk of harm. Decisions about appropriate levels of inducement will need to be justified to local research ethics committees.’ [Paragraph 6.32, and discussion 6.25–6.32]</p> <p><i>Other points:</i></p> <p>Uses concept of ‘genuine consent’ instead of ‘informed consent’: ‘Ensuring that consent is genuine requires care in detecting a lack of consent. The apparent genuineness of consent can be defeated by a number of circumstances, including coercion, deception, manipulation, deliberate misdescription of what has been proposed, lack of disclosure of material facts, or conflicts of interest. To obtain genuine consent, health professionals must do their best to communicate information accurately and in an understandable and appropriate way. The information provided to participants must be relevant, accurate and sufficient to enable a genuine choice to be made.’ [Paragraphs 6.4-6.5]</p>

¹ The concept of genuine consent was introduced by the NCOB in its 1995 Report, *Human Tissue: Ethical and Legal Issues*, paragraph 6.20.

Table 2: Guidance relating to standards of care

Guidance	Relevant sections	Text and notes
WMA 2000	Paragraph 29	<p><i>The standard of care that should be provided to the control group during research:</i></p> <p>‘The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.’ [Paragraph 29]</p> <p><i>The use of placebos:</i></p> <p>Placebos may be used only ‘for compelling and scientifically sound methodological reasons’ or when the risks to the participant and the condition being studied are minor. A ‘Note of clarification on Paragraph 29 re. the use of placebos’ was published in December 2002:</p> <p>‘The WMA reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available under the following circumstances:</p> <ul style="list-style-type: none"> - Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or - Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the participants who receive placebo will not be subject to any additional risk of serious or irreversible harm.’ [Note of clarification on Paragraph 29]
CIOMS 2002	Guideline 11	<p><i>The standard of care that should be provided to the control group during research:</i></p> <p>‘As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention. In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo or ‘no treatment’.’ [Guideline 11]</p> <p>New terminology was introduced in 2002: ‘established effective intervention’ used as a term for reference treatment, to include all current interventions, ‘including the best and the various alternatives to the best.’ [Introduction]</p>

Continued

Table 2: Guidance relating to standards of care *(continued)*

Guidance	Relevant sections	Text and notes
CIOMS 2002	Guideline 11	<p><i>The use of placebos:</i></p> <p>‘Placebo may be used:</p> <ul style="list-style-type: none"> • when there is no established effective intervention; • when withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms; • when use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects.’ [Guideline 11] <p>The commentary to Guideline 11 discusses the specific cases when the use of a placebo in place of an ‘established intervention’ may be morally justified. For example, a health authority in a country where an established effective intervention is not generally available or affordable, and unlikely to become available or affordable in the foreseeable future, may seek to develop an affordable intervention specifically for a health problem affecting its population.</p> <p>‘Ethical review committees will need to engage in careful analysis of the circumstances to determine whether the use of placebo rather than an established intervention is ethically acceptable. They will need to be satisfied that an established effective intervention is truly unlikely to become available and implementable in that country.’ [Guideline 11, Commentary]</p>
CoE 2004	Article 23	<p><i>The standard of care that should be provided to the control group during research:</i></p> <p>‘Research shall not deprive participants of necessary procedures... In research associated with prevention, diagnosis or treatment, participants assigned to control groups shall be assured of proven methods of prevention, diagnosis or treatment.’ [Article 23.2]</p> <p>‘It is expected that a proven method of treatment that is available in the country or region concerned be utilised.’ [Explanatory Report, paragraph 120]</p> <p><i>The use of placebos:</i></p> <p>‘The use of placebo is permissible where there are no methods of proven effectiveness, or where withdrawal or withholding of such methods does not present an unacceptable risk or burden.’ [Article 23.3]</p>

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Table 2: Guidance relating to standards of care (*continued*)

Guidance	Relevant sections	Text and notes
EU 2001	Article 19	<p>Does not address placebo-controlled trials or standard of care issues.</p> <p><i>The obligations of sponsors:</i></p> <p>'Unless Member States have established precise conditions for exceptional circumstances, investigational medicinal products and, as the case may be, the devices used for their administration should be made available free of charge by the sponsor.' [Article 19]</p>
EGE 2003	Paragraph 2.10, 2.12	<p><i>The use of placebos:</i></p> <p>'The use of placebos should be regulated in developing countries in principle by the same rules as in European countries. Any exception must be justified: an obvious one is when the primary goal of the clinical trial is to try to simplify or to decrease the costs of treatment for countries where the standard treatment is not available for logistic reasons or inaccessible because of cost. It may thus be justified to derogate from the rule of best proven treatment. The justification of using a placebo must be clearly demonstrated in the research protocol submitted to the ethical committees and especially approved by the local committee.' [Paragraph 2.10]</p> <p>It should be noted that 'two members of the Group recorded their dissent, considering 'that the use of placebo for the purpose of developing low cost treatment could mean accepting a 'double standard' for poor and rich countries.'</p> <p><i>The obligations of sponsors:</i></p> <p>Where research participants would not receive a standard of care because of its cost, it must be provided by the sponsor:</p> <p>'In industrialised countries, the reference treatment used in a clinical trial may be provided by the healthcare services, while the new drug being tested is provided by the sponsor. When a trial is implemented in a country or community where patients cannot benefit from the standard treatment because of the cost, it is then up to the sponsor to provide it.' [Paragraph 2.12]</p> <p>Paragraphs 1.24, 1.32, 1.34 and 2.10 also discuss the issues raised by the provision of different standards of care</p>
NCOB 2002	Chapter 7	<p><i>The standard of care that should be provided to the control group during research:</i></p> <p>Research below the universal standard of care can be justified in some cases.</p> <p>'We recommend that in setting the standard of care for the</p>

Continued

Table 2: Guidance relating to standards of care *(continued)*

Guidance	Relevant sections	Text and notes
NCOB 2002	Chapter 7	<p>control group of a particular research project the context in which the research is to be conducted be carefully evaluated. A suitable standard of care can only be defined in consultation with those who work within the country and must be justified to the relevant research ethics committees. Wherever appropriate, participants in the control group should be offered a universal standard of care for the disease being studied. Where it is not appropriate to offer a universal standard of care, the minimum standard of care that should be offered to the control group is the best intervention available for that disease as part of the national public health system.’ [Paragraph 7.29]</p> <p>‘In exceptional circumstances, research may be proposed which involves the use of a standard of care that is lower than the best available intervention as part of the host country’s public health system for the disease being studied. For example, researchers may wish to demonstrate that what is deemed to be the best treatment available through the host country’s public health system is ineffective, or even harmful, by comparing it to a placebo, or an apparently lesser standard of care... If an aim of research into healthcare is to improve current forms of treatment, then there may be circumstances in which it is justified to compare current local practice with a new treatment, in the local setting.’ [Paragraph 7.30]</p> <p>The Report also discusses standard of care as it relates to two more specific forms of research:</p> <ul style="list-style-type: none"> (a) research into preventive measures; and (b) trials comparing different standards of care. <p><i>The provision of care to all trial participants:</i></p> <p>‘We recommend that before research beings, agreement should be reached about the standard of care that should be provided to participants in research who already have or who develop diseases other than the disease being studied. We conclude that the minimum standard of care that should be offered is the best intervention available as part of the national public health system. Any proposal which contemplates care of a lower standard deviation must be justified to the relevant research ethics committee.’ [Paragraph 7.35]</p>

Table 3: Guidance relating to what happens after the research is over

Guidance	Relevant sections	Text and notes
WMA 2000	Paragraph 30	<p><i>Should post-trial treatment be provided?</i></p> <p>'At the conclusion of the study, every patient entered in the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods.' [Paragraph 30]</p> <p>A Note of clarification on Paragraph 30 was issued on May 2004: 'The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.' [Note of clarification on Paragraph 30]</p> <p><i>Who should supply treatment or provide interventions?</i></p> <p>Does not address who has an obligation to supply treatment.</p>
CIOMS 2002	Guideline 10	<p><i>Who should supply treatment or provide interventions?</i></p> <p>The sponsor should provide post-trial access to treatment: 'Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that:</p> <ul style="list-style-type: none"> - the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and - any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.' <p>[Guideline 10]</p> <p>The commentary on Guideline 10 clarifies the concepts of 'responsiveness' and 'reasonably available', stating that sponsors and investigators should consult with relevant stakeholders of the country where the research is to take place, 'including the national government, the health ministry, local health authorities, concerned scientific and ethics groups, non-governmental organisations such as health advocacy groups, and representatives of the communities of those who might participate in the study.' [Guideline 10, Commentary]</p> <p>'The issue of "reasonable availability" is complex and will need to be determined on a case-by-case basis. Relevant considerations include the length of time for which the intervention or product developed, or other agreed benefit, will be made available to research subjects, or to the</p>

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Table 3: Guidance relating to what happens after the research is over (*continued*)

Guidance	Relevant sections	Text and notes
CIOMS 2002	Guideline 10	community or population concerned; the severity of a subject's medical condition; the effect of withdrawing the study drug (e.g., death of a subject); the cost to the subject or health service; and the question of undue inducement if an intervention is provided free of charge.' [Guideline 10, Commentary]
CoE 2004		Does not address the issue. The Appendix to the Protocol, which covers information to be given to the research ethics committee, does not stipulate that information about post-trial access to treatment is required or should be provided to participants during the consent process.
EU 2001		Does not address the issue.
EGE 2003	Paragraph 2.13	<i>Should post-trial treatment be provided?</i> Requires provision of successful treatment to all participants upon completion of the trial, even if treatment would need to be provided for a lifetime: 'In industrialised countries, free supply of a proven beneficial new drug to all the participants of a trial after the trial is ended is the rule as long as it is not yet available through the normal health care system. In developing countries, the same rule must be applicable even if this implies supplying the drug for a lifetime if necessary. Moreover, there should be an obligation that the clinical trial benefits the community that contributed to the development of the drug. This can be e.g. to guarantee a supply of the drug at an affordable price for the community or under the form of capacity building. The protocol of clinical trials must specify who will benefit, how and for how long.' [Paragraph 2.13] <i>Who should supply treatment or provide interventions?</i> However, EGE 2003 does not address who should be responsible for supplying treatment or maintaining relevant facilities.
NCOB 2002	Chapter 9	<i>Should post-trial treatment be provided?</i> Acknowledges that it may not be possible in all cases to ensure post-trial access and suggests that possible post-trial treatment options should be clarified before the trial begins: 'We endorse the 2001 National Bioethics Advisory Commission's (NBAC) recommendation that researchers should

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Table 3: Guidance relating to what happens after the research is over *(continued)*

Guidance	Relevant sections	Text and notes
NCOB 2002	Chapter 9	<p>endeavour before the initiation of a trial to secure post-trial access for effective interventions for participants in the trial and that the lack of such arrangements should have to be justified to a research ethics committee.' [Paragraph 9.31]</p> <p><i>Who should supply treatment or provide interventions?</i></p> <p>Does not address who will supply treatment:</p> <p>'Responsibility for making a vaccine, treatment or other intervention available will not lie solely with any one group. If a national government has agreed to allow a trial to take place, it presumably accepts some responsibility to act on the results. However, some form of external aid or subsidy may be necessary before any intervention can be made more widely available and there will need to be negotiations between the various interested parties.' [Paragraph 9.36]</p>

Table 4: Guidance relating to ethical review

Guidance	Relevant sections	Text and notes
WMA 2000	Paragraph 13	<p>'The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.' [Paragraph 13]</p> <p>Does not require a separate scientific review committee or discuss where review should take place.</p>
CIOMS 2002	Guidelines 2, 3, 20	<p><i>Should there be separate scientific and ethical review?</i></p> <p>Scientific review does not need to be performed by a separate review committee:</p> <p><i>'Ethical and scientific review:</i> Committees in both the country of the sponsor and the host country have responsibility for conducting both scientific and ethical review, as well as the authority to withhold approval of research proposals that fail to meet their scientific or ethical standards.'<i>' [Guideline 3, Commentary]</i></p> <p><i>Where should review take place?</i></p> <p>While Guideline 2 discusses ethics review committees, Guideline 3 specifically addresses ethical review of externally sponsored research. Review should take place in both sponsoring and host country, although a host country is not always required to have a distinct fully functional REC in all cases:</p> <p><i>'An external sponsoring organization and individual investigators should submit the research protocol for ethical and scientific review in the country of the sponsoring organization, and the ethical standards applied should be no less stringent than they would be for research carried out in that country. The health authorities of the host country, as well as a national or local ethical review committee, should ensure that the proposed research is responsive to the health needs</i></p>

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Table 4: Guidance relating to ethical review *(continued)*

Guidance	Relevant sections	Text and notes
CIOMS 2002	Guidelines 2, 3, 20	<p>and priorities of the host country and meets the requisite ethical standards.’ [Guideline 3]</p> <p>‘When a sponsor or investigator in one country proposes to carry out research in another, the ethical review committees in the two countries may, by agreement, undertake to review different aspects of the research protocol ... The ethical review committee in the host country can be expected to have greater competence for reviewing the detailed plans for compliance, in view of its better understanding of the cultural and moral values of the population in which it is proposed to conduct the research ... However, in respect of research in host countries with inadequate capacity for independent ethical review, full review by the ethical review committee in the external sponsoring country or international agency is necessary.’ [Guideline 3, Commentary]</p> <p><i>Funding and support for a REC in the host country:</i></p> <p>‘The review committees must be independent of the research team, and any direct financial or other material benefit they may derive from the research should not be contingent on the outcome of their review.’ [Guideline 2]</p> <p>‘The regulatory or other governmental authorities concerned should promote uniform standards across committees within a country, and, under all systems, sponsors of research and institutions in which the investigators are employed should allocate sufficient resources to the review process. Ethical review committees may receive money for the activity of reviewing protocols, but under no circumstances may payment be offered or accepted for a review committee’s approval or clearance of a protocol.’ [Guideline 2, Commentary]</p> <p>Sponsoring countries have a responsibility to support the building of capacity of RECs in developing countries. However, the guideline does not state whether this contribution should be provided to the host country directly or indirectly:</p> <p>‘Many countries lack the capacity to assess or ensure the scientific quality or ethical acceptability of biomedical research proposed or carried out in their jurisdictions. In externally sponsored collaborative research, sponsors and investigators have an ethical obligation to ensure that biomedical research projects for which they are responsible in such countries contribute effectively to national or local capacity to design and conduct biomedical research, and to provide scientific and ethical review and monitoring of such research.’ [Guideline 20]</p>

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Table 4: Guidance relating to ethical review (*continued*)

Guidance	Relevant sections	Text and notes
CIOMS 2002	Guidelines 2, 3, 20	<p>‘External sponsors and investigators have an ethical obligation to contribute to a host country’s sustainable capacity for independent scientific and ethical review and biomedical research.’ [Guideline 20, Commentary]</p> <p>Recommendation 5.7 of the NBAC 2001 guidelines concurs: ‘Where applicable, U.S. sponsors and researchers should assist in building the capacity of ethics review committees in developing countries to conduct scientific and ethical review of international and collaborative research.’²</p> <p><i>Role of a REC after the approval of research:</i></p> <p>‘The ethical review committee should conduct further reviews as necessary in the course of the research, including monitoring of the progress of the study.’ [Guideline 2]</p>
CoE 2004	Article 7, 9 – 12, 29	<p><i>Should there be separate scientific and ethical review?</i></p> <p>Supports a scientific review of research protocols, by a ‘competent body’ (separate from discussion of ethical review):</p> <p>‘Research may only be undertaken if the research project has been approved by the competent body after independent examination of its scientific merit, including assessment of the importance of the aim of research, and multidisciplinary review of its ethical acceptability.’ [Article 7]</p> <p>‘It is acknowledged that in some countries, the ethics committee could also act as the competent body while in other cases or in other countries, the competent body might be a Ministry or a regulatory agency, which would take the opinion of the ethics committee into account.’ [Explanatory Report, paragraph 28]</p> <p><i>Where should review take place?</i></p> <p>Each State in which any research activity takes place should provide ethical review and an Appendix lists the information that should be given to the ethics committee for consideration:</p> <p>‘Every research project shall be submitted for independent examination of its ethical acceptability to an ethics committee. Such projects shall be submitted to independent examination in each State in which any research activity is to take place.’ [Article 9]</p>

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² National Bioethics Advisory Commission (2001) *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries* (Bethesda: NBAC).

Table 4: Guidance relating to ethical review (continued)

Guidance	Relevant sections	Text and notes
CoE 2004	Article 7, 9 – 12, 29	<p>Article 29 considers the possibility that research might take place in a country which is not a member of the Protocol, or in a country where no suitable body for the review of research exists. In such cases, the sponsors or researchers:</p> <p>‘shall ensure that, without prejudice to the provisions applicable in that state, the research project complies with the principles on which the provisions of this Protocol are based. Where necessary, the [sponsors and researchers] shall take appropriate measures to that end.’ [Article 29]</p> <p>‘In addition to complying with all the conditions applicable in the State in the territory of which the research is to be undertaken, the principles on which the provisions of this Protocol are based must be complied with... For example, there may not be a body capable of undertaking appropriate independent scientific and ethical evaluation of research in the country, but the principle of the research project being submitted to an independent body for review must be observed this does not imply that a body in the state Party to the Protocol has the authority to approve research in the non-Party State if that State does not approve the research, or to override its regulations.’ [Explanatory Report, paragraph 138]</p> <p>‘In the case where the research must be undertaken in States not having well established systems of protection, the provisions could foresee the obligation to submit the research project to an ethics committee of the Party concerned.’ [Explanatory Report, Paragraph 140]</p> <p><i>Funding and support for a REC in the host country:</i></p> <p>‘Parties to this Protocol shall take measures to assure the independence of the ethics committee. That body shall not be subject to undue external influences.’ [Article 10]</p>
EU 2001	Article 3, 6, 9	<p><i>Should there be separate scientific and ethical review?</i></p> <p>Implication that the ethics review should include both scientific and ethical review:</p> <p>‘The ethics committee shall consider...</p> <p>(a) the relevance of the clinical trial and the trial design...</p> <p>(c) the protocol...’ [Article 6.3 a-c]</p> <p><i>Where should review take place?</i></p> <p>A single ethical opinion should be given by each state participating in the trial and a competent authority in the host country:</p>

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Table 4: Guidance relating to ethical review (*continued*)

Guidance	Relevant sections	Text and notes
EU 2001	Article 3, 6, 9	<p>'A clinical trial may be initiated only if the Ethics Committee and/or competent authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored.' [Article 3.2 a]</p> <p>'The sponsor may not start a clinical trial until the Ethics Committee has issued a favourable opinion inasmuch as the competent authority of the Member State concerned has not informed the sponsor of any grounds for non-acceptance.' [Article 9]</p> <p><i>Funding and support for a REC in the host country:</i> Discussion not necessarily related to trials outside EU countries, but states that: 'For the purposes of implementation of the clinical trials, Member States shall take the measures necessary for establishment and operation of Ethics Committees.' [Article 6.1]</p>
EGE 2003	Paragraph 2.8	<p><i>Should there be separate scientific and ethical review?</i> EGE 2003 does not require a separate scientific review committee. Issues that should be considered during evaluation of a research protocol are listed in paragraph 2.9.</p> <p><i>Where should review take place?</i> 'The scientific and ethical evaluation of the research protocol should be carried out by ethical committees from all countries involved. Host countries need to have a legal and ethical framework in order to take part in the clinical trial evaluation effectively and independently... When no local ethics committee exists, then the evaluation should be done by a mixed committee involving representatives from both EU Member States and host countries. It is essential that the members of this committee are independent and include persons representing participants' interests. If it is not possible to involve such an independent local representative in the evaluation, then no clinical trial should be implemented in the country.' [Paragraph 2.8]</p> <p><i>Funding and support for a REC in the host country:</i> 'The group strongly supports EU initiatives to build local ethical committees in the host countries. It should be considered as a priority in terms of capacity building.' [Paragraph 2.8]</p>

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Table 4: Guidance relating to ethical review *(continued)*

Guidance	Relevant sections	Text and notes
NCOB 2002	Chapter 8	<p><i>Should there be separate scientific and ethical review?</i></p> <p>A separate scientific committee should conduct a scientific review:</p> <p>‘There are concerns that, in a single ethics committee, the distinction between the review of the science and the ethics, which have quite different purposes, may be ill defined... We conclude that these two forms of review should, where possible, be kept separate. This may, but will not necessarily, require the establishment of separate committees.’ [Paragraph 8.5]</p> <p><i>Where should review take place?</i></p> <p>Separate ethical reviews should take place in both countries:</p> <p>‘We recommend that externally sponsored research projects should be subject to independent ethical review in the sponsor’s country(ies) in addition to the country(ies) in which the research is to be conducted.’ [Paragraph 8.22]</p> <p>‘all developing countries should have in place a properly constituted and functioning system for the independent ethical review of research. This will include the establishment of effective research ethics committees.’ [Paragraph 8.16]</p> <p><i>Funding and support for a REC in the host country:</i></p> <p>‘Developing countries may determine that the most appropriate means of reviewing externally-sponsored research is via an independent national research ethics committee. In such circumstances the establishment, funding and proper operation of independent national research ethics committees should be the responsibility of national governments. No research should be conducted without review at the national or local level.’ [Paragraph 8.16]</p> <p>‘We conclude that there is a need for creative approaches to providing support, especially financial support, for research ethics committees, without compromising their independence. Sponsors should determine how they can meet the costs of ethical review without compromising the independence of the research ethics committee and should be responsible for meeting the costs of reviewing externally-sponsored research.’ [Paragraph 8.20]</p>

Appendix B: Internet addresses of guidance

■ World Medical Association (WMA):

Declaration of Helsinki as last revised in Oct 2000; Notes of clarification on Paragraph 29 and Paragraph 30 added 2002 and 2004: <http://www.wma.net/e/policy/b3.htm>

■ The Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO):

International Ethical Guidelines for Biomedical Research Involving Human Subjects, as last revised in Sep 2002; http://www.cioms.ch/frame_guidelines_nov_2002.htm

■ Steering Committee on Bioethics (CDBI) of the Council of Europe (CoE):

Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, adopted by the Committee of Ministers, June 2004; <http://conventions.coe.int/Treaty/EN/Projets/Protocol-Biomedical%20research.htm#>

■ European Council and European Parliament (EU):

Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, April 2001, adopted by Member States by May 2003, brought into force May 2004; http://europa.eu.int/eur-lex/pri/en/oj/dat/2001/l_121/l_12120010501en00340044.pdf

■ The European Group on Ethics in Science and New Technologies (EGE):

Opinion Nr 17 on the ethical aspects of clinical research in developing countries, published in Jan 2003; http://europa.eu.int/comm/european_group_ethics/docs/avis17_en.pdf

■ Nuffield Council on Bioethics:

The ethics of research related to healthcare in developing countries, April 2002; <http://www.nuffieldbioethics.org/developingcountries>

Appendix C: Workshop programme and delegates

12–14th February 2004
Cape Town, South Africa

DAY ONE: Thursday 12th February

OPENING PLENARY		
9.00	Welcome and introduction	Professor William Pick <i>Acting President, SA MRC</i>
		Professor Sir Bob Hepple QC <i>Chairman of Nuffield Council on Bioethics</i>
9.15	Comparison of guidelines <i>Based on background paper</i>	Professor Sir Kenneth Calman KCB FRSE, <i>Nuffield Council on Bioethics and Chairman of the Working Party on the ethics of research related to healthcare in developing countries</i>
	Discussion	
SESSION I: CASE STUDIES		
10.00	Acute disease <i>Case study: malaria</i>	Speaker: Professor Malcolm Molyneux, <i>Wellcome Trust Unit, Malawi</i>
		Discussant: Dr Tumani Corrah <i>MRC Laboratories, The Gambia</i>
10.45	BREAK	
11.15	Chronic disease <i>Case study: developing guidelines for HIV vaccine trials in South Africa</i>	Speaker: Ms Catherine Slack, <i>HIV AIDS Vaccines Ethics Group (HAVEG), South Africa</i>
		Discussant: Professor Carlos Brites, <i>Head, Retroviral Laboratory, Federal University of Bahia, Brazil</i>
12.00	Preventive treatments <i>Case study: rotavirus vaccines</i>	Speaker: Dr Roger Glass, <i>CDC, US</i>
		Discussant: Dr Job Bwayo, <i>Kenya AIDS vaccine initiative, University of Nairobi, Kenya</i>
12.45	LUNCH	

SESSION II: BREAKOUT GROUPS I

2.00 Introduction Professor Peter Smith,
*London School of Hygiene and
Tropical Medicine and Nuffield
Council on Bioethics*

In-depth discussion of issues raised in guidance

2.15	1	2	3	4
	Consent	Standards of care	Once research is over	Ethical Review (including research priorities)

*Chairs: members of Steering Committee. Rapporteurs to be selected.
Feedback for each group will take place on Day Two.
BREAK between 3.30 – 4.00pm*

SESSION III: PLENARY

5.15 Research Priorities Speaker:
Mr Tim Martineau,
Senior Health Advisor, DFID

Discussant:
Professor Terrence Forrester, *Tropical Medicine
Research Institute, University of West Indies*

6.30 RECEPTION

DAY TWO: Friday 13th February

SESSION IV: BREAKOUT GROUPS II

9.00	1	2	3	4
	Consent	Standards of care	Once research is over	Ethical Review (including research priorities)

In-depth discussion as on Day One. Delegates will take part in different Breakout Groups on each day.

BREAK between 10.45 – 11.15am

12.30 LUNCH

SESSION V: FEEDBACK FROM BREAKOUT GROUPS AND DISCUSSION

Chair: Professor Peter Smith

2.00	Feedback: Consent	Group I Rapporteur Group II Rapporteur Discussion
2.45	Feedback: Standards of care	Group I Rapporteur Group II Rapporteur Discussion
3.30	BREAK	
4.00	Feedback: Once the research is over	Group I Rapporteur Group II Rapporteur Discussion
4.45	Feedback: Ethical review	Group I Rapporteur Group II Rapporteur Discussion

DAY THREE: Saturday 14th February**SESSION VI: USER PERSPECTIVES**

To discuss the impact of developments and revisions to guidelines for each of the three main user groups (researchers, reviewers and sponsors)

9.00	Researchers	Professor Jimmy Whitworth, <i>London School of Hygiene and Tropical Medicine</i> Dr Athula Sumathipala, <i>Director, Bioethics initiative, Forum for Research and Development, Sri Lanka</i> Discussion
9.30	Ethical Reviewers	Dr Asad Raja, <i>Chairman Ethics Review Committee, Aga Khan University</i> Dr Kim Mulholland, <i>Centre for International Child Health, Australia</i> Discussion
10.00	Sponsors	Dr Nadia Tornieporth, <i>Clinical Development Prophylactic Vaccines, GSK Biologicals</i> Dr Imogen Evans, <i>MRC</i> Discussion

BREAK

SESSION VII: NEXT STEPS

To explore areas which have not yet received significant discussion and to anticipate future developments

11.15	Case study: Collecting biological samples	Professor Dominic Kwiatkowski, <i>Oxford University</i> Discussant: Dr Charles Rotimi, <i>HapMap, Nigeria</i>
12.00	Summing up and conclusion	Professor Catherine Peckham, <i>Nuffield Council on Bioethics</i> Professor Denie DuToit, <i>Chairman, SA MRC ethics committee</i>
CLOSE OF WORKSHOP		
12.30	LUNCH	

List of delegates

Name	Organisation*	Country
Dr Angelica ANGELES	National Institute of Public Health (NIPH), Cuernavaca, Morelos	Mexico
Ms Gayane ASLANYAN	Armenian Drug and Medical Technology Agency	Armenia
Professor Solly BENATAR	International Research Ethics Network for Southern Africa (IRENSA), University of Cape Town	South Africa
Professor Zulfiqar BHUTTA	Professor of Paediatrics, Aga Khan University	Pakistan
Professor Carlos BRITES	Associate Professor of Infectious Diseases Head, Retrovirus Laboratory, Federal University of Bahia	Brazil
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* Positions at time of Workshop, February 2004.

Appendix D: Background literature

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Glossary

Acquired Immune Deficiency Syndrome (AIDS): A disease caused by retroviral infection with the human immunodeficiency virus (HIV-1, HIV-2). The disease leads to failure of the immune system and debilitation, and is often accompanied by infections such as tuberculosis. The disease is transmitted through direct contact with bodily fluids (e.g. blood-blood or via sexual intercourse).

Aetiology: Study of the causes or origins of a disease or abnormal condition.

Antigen: A foreign molecule that triggers an antibody response.

Anti-retroviral therapy: A group of medicines used in the treatment of HIV/AIDS.

Cerebrospinal meningitis: Cerebrospinal meningitis or meningococcal meningitis is a contagious disease caused by the bacteria *meningococcus*. It causes both sporadic and **epidemic** outbreaks, predominantly in children and young adults. The disease is characterised by inflammation of the meninges (three layers of connective tissue that envelop the brain and spinal cord); the symptoms include severe headache, photophobia (light sensitivity) and neck stiffness. The disease can be severe with high mortality rates, or result in permanent neurological disability.

Clinical research and clinical trials: Medical research studies designed to answer scientific questions and to find better ways to prevent, detect, or treat disease. A large number of clinical trials are confined to testing the safety and efficacy of new medicines. There are generally four separate phases of such trials:

- **Phase I trials:** Phase I studies will be the first time human subjects are exposed to the potential new medicine. The objectives of the study will be to investigate pharmacodynamics, dose-response, and in the case of vaccines, immune response, and to determine the maximum dose that can be tolerated by participants. In the case of most new medicines these studies will be undertaken in a small number of healthy volunteers. Evidence for the efficacy of the medicine would not normally be provided by Phase I studies.
- **Phase II trials:** Using the information about the safe dosage range obtained from the Phase I studies, the compound will be administered to patients suffering from the target disease. Significant numbers of individuals will be recruited into the trial at a number of clinical centres. The objective of the Phase II studies will be to seek evidence of the efficacy of the medicine against the specific disease. More information about the safety of the medication will emerge from these studies as larger numbers of individuals are exposed to the medicine. In Phase II trials, the patient will often be randomly assigned to the novel treatment group or to a group receiving a placebo (a compound possessing no therapeutic effect) or, more usually, a conventional and established treatment.
- **Phase III trials:** Where a compound has shown evidence of efficacy without significant side effects, it will enter Phase III trials. Many hundreds, or sometimes a few thousand patients will be enrolled. These trials will generally seek not only to confirm the clinical efficacy of the novel compound, but also to establish its efficacy in comparison to existing treatments. These studies will often be multicentre and sometimes undertaken on an international basis. Again, careful attention is paid to possible side effects as larger numbers of patients are exposed to the intervention. The end-points for Phase III studies include the demonstration of a statistically significant improvement in the efficacy of the novel medicine over the established therapies, if any such exist.
- **Phase IV trials:** Once a new medicine reaches the market it will be subjected to post-marketing surveillance in order to identify side-effects and other adverse effects which would only become evident as much larger numbers of individuals are treated. In addition,

formal clinical trials continue in order to develop a greater understanding of the compound and its effects in a wider clinical environment. Further study may also extend its use for other indications or for different patient groups, such as children or the elderly. Special study designs may be used according to the objectives of the study to evaluate safety or efficacy. These may include study of temporal trends, case-control studies, or the phased introduction of an intervention in different areas. Phase IV studies may also be designed to measure the impact of the intervention on the **epidemiological** pattern or the transmission of an **infectious disease**.

Conjugate: Paired together, such as in pneumococcal conjugate vaccines for pneumonia and meningitis.

Control: A control group in **clinical research and clinical trials** contains participants who are not given the intervention which is being tested in the research. The results of the control group will be compared with a group who are given the intervention. In clinical trials, the intervention would normally be a novel treatment, such as a medicine or vaccine. Interventions may also be social and behavioural in nature, such as, safe sex campaigns.

Epidemic: A temporary increase in the prevalence of a disease within a specific community or region. The rise in prevalence may last a few weeks or years.

Epidemiological research: Research concerned with describing and explaining the occurrence of disease in populations.

Haplotype: A specific combination of linked alleles in a cluster of related genes. An allele is a variant form of a gene, which differs in DNA sequence from alternative alleles of the same gene.

HapMap: An international project established in 2002 to create a haplotype map of the human genome. The project will describe the common patterns of human DNA sequence variation and may be used to identify genes linked to susceptibilities to disease. Researchers from Canada, China, Japan, Nigeria, the UK and US expect to complete the map by 2005.

Hepatitis B: A virus transmitted through 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 develop into chronic hepatitis. Symptoms include tiredness, sickness, fever, loss of appetite, stomach pains, and diarrhoea. Symptoms may also include dark yellow urine, and yellowish eyes and skin (also called jaundice).

Hib disease: Hib disease is a group of diseases caused by the *Haemophilus influenzae* type B bacteria e.g. pneumonia and bacterial meningitis.

Hib polysaccharide – protein conjugate vaccine: A vaccine for *Haemophilus influenzae* type B containing a 'weak' polysaccharide (complex naturally occurring carbohydrates e.g. starch) linked to a protein.

Hypertension: Persistently high arterial blood pressure, which may have no known cause or be associated with other diseases. Hypertension is a risk factor for the development of diseases such as heart disease and stroke.

Infectious diseases: Infectious or communicable diseases are caused by living organisms, mainly micro-organisms (e.g. viruses, bacteria and fungi and groups intermediate between viruses and bacteria e.g. chlamydiae). The source of disease can be another human, animal or insect. Transmission occurs via several routes (e.g. physical contact, food and drink) and organisms typically enter the body by inhalation or direct contact.

Ivermectin: One of a class of medicines used to treat infestation with several species of nematode worms transmitted by biting insects. It is used as the medicine of choice for the treatment of **onchocerciasis**.

Morbidity: Levels of sickness and ill health.

Non-communicable diseases: Diseases caused by factors other than living organisms, such as lifestyle, diet, genes or a combination of factors. Examples of non-communicable diseases include mental disorders, heart disease, and cancer.

Non-infectious diseases: See *non-communicable diseases*.

Onchocerciasis ('River Blindness'): Onchocerciasis is a parasitic disease transmitted by simuliid flies, which breed in fast-flowing rivers and streams. The parasites migrate to different parts of the human body, including to the eyes where they may cause blindness.

Perinatal transmission: Transmission of an infection-causing agent, such as HIV, from mother to child in the period either shortly before or after birth.

Primary endpoint (of a clinical trial): The principal result that is measured at the end of a study to establish whether a given treatment was effective.

Prophylactic: Preventive measure, including medication.

Randomised controlled trials: An experiment in which investigators randomly allocate eligible participants into **control** and intervention groups to receive one or more interventions that are being tested. The results are assessed by comparing outcomes of the two groups.

Rectal artesunate: An anti-malarial medicine administered as a suppository.

Rotavirus vaccines: Vaccines for immunisation against rotavirus, the commonest cause of severe diarrhoea among children worldwide.

Serotype: A group of closely related microorganisms (including bacteria, viruses, fungi and protozoa) distinguished by a characteristic set of **antigens**.

Glossary of abbreviations

AIDS	Acquired Immune Deficiency Syndrome
ART	Anti-Retroviral Treatment/Therapy
CAB	Community Advisory Board
CDBI	Steering Committee on Bioethics of the Council of Europe
CIOMS	Council for International Organizations of Medical Sciences
CoE	Council of Europe
CONEP	National Ethics in Research Committee (Brazil)
DEC	Diethylcarbamazine
DNA	Deoxyribonucleic acid
DTP-Hib	Combination vaccine: diphtheria, tetanus, pertussis and <i>Haemophilus influenzae</i> type B
EGE	European Group on Ethics in Science and New Technologies
EU	European Union
FDA	United States Food and Drug Administration
HIV	Human Immunodeficiency Virus
IAVI	International AIDS Vaccine Initiative
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND	Investigational New Drug
ITNs	Insecticide-treated nets
KAVI	Kenya AIDS Vaccine Initiative
MDG	Millennium Development Goals
MRC	Medical Research Council
NBAC	National Bioethics Advisory Commission (US)
NCD	Non-Communicable Disease
NCOB	Nuffield Council on Bioethics (UK)
NIH	National Institutes of Health (US)
PABIN	Pan-African Bioethics Initiative
RECs	Research Ethics Committees
SA MRC	Medical Research Council of South Africa
SIDCER	Strategic Initiative for Developing Capacity in Ethical Review
UNAIDS	Joint United Nations Programme on HIV/AIDS
US	United States
WHO	World Health Organization
WMA	World Medical Association

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