Chapter 5

The framework of guidance

Introduction

5.1 The conduct of research related to healthcare is subject to a wide range of national and international guidance, guidelines, declarations and regulations (which we will call guidance, except for those regulations which have the force of law). The international guidance has formed the basis for the national guidance adopted in many countries. In general, the guidance covers a wide range of activities in research involving human participants. In Chapter 4, we set out four principles that should guide decision-making in the conduct of research related to healthcare in developing countries, which is sponsored by other, developed countries: the duty to alleviate suffering, the duty to show respect for persons, the duty to be sensitive to cultural differences, and the duty not to exploit the vulnerable. These principles are reflected in the various forms of guidance but are sometimes expressed in different ways. For example, respect for persons is sometimes expressed more narrowly as respect for individual autonomy. The duty to alleviate suffering is sometimes referred to in terms of beneficence, or a duty to benefit other people, and the duty not to exploit the vulnerable encompasses guidance expressed in terms of fairness and justice.

5.2 In addition, two common themes arise in the various forms of guidance. The first is the need for research to be based on sound scientific principles, on knowledge derived from laboratory and animal experiments, if appropriate, and on a sound understanding of the scientific literature. The second is the need to ensure that the results of research are accurately reported and published, that publication can only take place where it can be demonstrated that ethical principles relevant to the conduct of research have been observed, and that negative as well as positive results are reported.

5.3 Over recent years, there has been increasing criticism of much of the guidance which exists on two counts. First, while such guidance sets out the fundamental ethical principles relevant to the conduct of clinical research on human participants, it is too general in nature to address many of the specific and often controversial issues that are raised by such research. For example, guidance about the standards of care which should be used in clinical trials and the availability of treatment after a trial is over is set out in very general terms and has been subject to varying interpretations.[1]

5.4 Secondly, the various forms of guidance, whether international or national, in many instances do not take into account the special circumstances that attend research undertaken in developing countries and sponsored by developed countries. In addition developing countries often have little or no relevant national guidance. In such situations, where research is externally sponsored, there is a danger that the conduct of the research may fail to reflect the cultural and social values of those from the developing countries who participate. In this chapter, we review the broad framework of guidance which concerns research related to healthcare and consider how the specific issues raised by externally-sponsored research are addressed.

The historical context

5.5 During the last century, there have been a number of notorious cases in which participants have been harmed as a consequence of unethical clinical research. The Nuremberg Code was formulated in 1947 following the Nuremberg trials, at which a number of Nazi researchers were convicted. The trials revealed that research on human beings had been conducted by Nazi physicians in Germany without due regard to the welfare or, indeed, the survival of the

1 In the debate concerning the 'standard of care' in the perinatal HIV transmission studies (see Box 1.2), both sides cited the CIOMS 1993 guidelines to support their position. Debate centred on the question of whether the 'best proven diagnostic and therapeutic method' (Article II:3 of the 1996 Declaration of Helsinki) should take local resource considerations into account.

participants. The central feature of the Nuremberg Code was the protection of the integrity of the person participating in research. The Nuremberg Code was endorsed by the World Medical Association (WMA), which published the Declaration of Helsinki in 1964. The Declaration, which has been revised five times to date (Table 5.1 and Appendix 1), sets out the principles to be observed in research on human participants and has become the cornerstone of research related to healthcare. Its standing is such that the principles enshrined in it have been incorporated into many of the forms of guidance that have subsequently been drawn up to govern the conduct of research related to healthcare (see Table 5.1 for international guidance and Appendix 1, Table 1 for national guidance).

Table 5.1

International guidance for the conduct of research related to healthcare

Year	Organisation	Title
1947	War crimes tribunal at Nuremberg	Nuremberg Code
1948	United Nations General Assembly	Universal Declaration of Human Rights
1964	World Medical Association (WMA)	Declaration of Helsinki (1)
1975	WMA	Declaration of Helsinki (2) Tokyo
1983	WMA	Declaration of Helsinki (3) Venice
1989	WMA	Declaration of Helsinki (4) Hong Kong
1991	CIOMS/WHO	International Guidelines for Ethical Review of Epidemiological Studies
1993	CIOMS/WHO	International Ethical Guidelines for Biomedical Research Involving Human Subjects (Under revision in 2001–2)
1995	WHO	Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products
1996	WMA	Declaration of Helsinki (5) South Africa
1996	International Conference on Harmonisation (ICH)	Harmonised Tripartite Guideline. Guideline for Good Clinical Practice
1997	Council of Europe	Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine
1997	UNESCO	Universal Declaration on the Human Genome and Human Rights
2000	European Union	Charter of Fundamental Rights of the European Union
2000	UNAIDS	Ethical Considerations in HIV Preventive Vaccine Research
2000	WHO	Operational Guidelines for Ethics Committees that Review Biomedical Research
2000	WMA	Declaration of Helsinki (6) Edinburgh
2001	European Parliament and Council of the European Union	Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

International guidance for the conduct of research

5.6 The potential risk of harm to participants in research related to healthcare has led to widespread agreement that rigorous safeguards should be established irrespective of the geographic and economic setting in which it is undertaken. The present regime of guidance has developed largely in response to problems that have been encountered during the evolution of research related to healthcare. The major sources of international guidance have undergone, or are in the process of undergoing, revisions and development, but these revisions have generally been initiated to address specific shortcomings.

5.7 The implementation of guidance is the responsibility of those who are in contact with, or responsible for, participants in research. They will include government officials, aid agencies, institutional researchers, administrators and researchers, public and private sponsors of research, the senior management of companies, and research ethics committees. Ultimately, responsibility for observing and applying the guidance falls to those actively engaged in carrying out research involving human participants in the clinic, ward, laboratory or elsewhere. It is therefore important that guidance is written in terms which encourage consistent interpretation and which can be applied with confidence.

5.8 The guidance ranges from guidelines which claim general applicability, such as the Declaration of Helsinki and the guidelines of the Council for International Organizations of Medical Sciences (CIOMS)[2] to those with more narrow remits such as those set out in the **International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use** (ICH) which apply to the pharmaceutical industry, or **Ethical Considerations in HIV Preventive Vaccine Research** published by UNAIDS, which apply specifically to research into vaccines for a single disease (HIV/AIDS). In the next two sections, we consider how the Declaration of Helsinki and the CIOMS Guidelines apply in the context of research sponsored by developed countries and conducted in developing countries.

The Declaration of Helsinki

5.9 When the Declaration of Helsinki was published in 1964, the scope of its provisions was considered to be comprehensive. The Declaration established a set of basic principles from which were derived some general rules of conduct. The current revision (2000) recognises that the purpose of biomedical research involving human participants must be to 'improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease' and further, that medical progress is based on research that must at some stage involve human participants (see Box 5.1).

5.10 According to the current version (2000) of the Declaration, any research carried out involving human participants must be based upon sound scientific principles, and according to a properly formulated protocol for the study that has been subjected to the scrutiny and advice of an independent committee (i.e. a research ethics committee). The Declaration recognises the fact that most interventions – diagnostic, therapeutic and preventative – and especially those involving biomedical research, involve hazards and that the issues of risk and hazard must be addressed. It notes that when research involves healthy volunteers, special care must be taken to determine if the objective of the research outweighs the inherent risks and burdens to participants. The Declaration pays particular attention to the problems that may arise where research is combined

2 The guidelines were developed in collaboration with WHO.

BOX 5.1 Revisions to the Declaration of Helsinki

The Declaration of Helsinki has been revised five times by the WMA since its initial adoption in 1964. The revision in 1996 was accompanied by considerable debate and within a year, the American Medical Association (AMA) had proposed another significant revision. In addition to including a consideration of research in developing countries, the draft revision amended or expanded guidance relating to consent and review of the ethics of research, the involvement of pregnant women in research, possible conflicts of interest, data and confidentiality, and the publication of research results.

As the Declaration is considered to be the pre-eminent guidance on ethical principles in research relating to healthcare, there was criticism of the process for such a substantial revision of the Declaration, which had been restricted to members of the WMA. In response to this criticism, the draft revision proposed by the AMA was circulated for public comment. Concerns were expressed that a number of protections for participants in research were being minimised or removed. These included provisions relating to the standards of care provided to participants in research, responsibility for participants in research and publication of research results.[1] Those in favour of substantial revision argued that these provisions and others were not relevant to a number of situations in research, and were frequently breached. It was proposed that the guidance be updated so that it took greater account of current practice. A counter-argument was that it was the current practice that was unethical and the guidance needed only minor revision. Rather than substantially rewriting the fundamental guidance relating to research related to healthcare, it was claimed that the Declaration should continue to evolve slowly, with minimal amendments, and focus on setting out fundamental principles, about which there was broad agreement. Guidance about the application of principles could then be provided in accompanying commentaries, which could be updated more frequently.[2]

The revision proposed by the AMA was rejected and the WMA charged a committee with the task of putting together a new draft. This was circulated for comment, and adopted as a revision to the Declaration at the WMA meeting in Edinburgh in 2000. It was greeted with approval from critics of the AMA draft.[3] However, a number of organisations have since claimed that paragraph 29 (concerning standards of care provided to participants in research) and paragraph 30 (concerning what happens once research is over) of the revised Declaration are inappropriate. The WMA has recently published a note of clarification for paragraph 29 (Table 5.2).

1 Anon (1999) Helsinki Declaration revising continues, **Bulletin of Medical Ethics**, 146 3–5.
2 Review (1999) Revising the Declaration of Helsinki: a fresh start, **Bulletin of Medical Ethics**, 151 13–17.
3 For example, commentators from Public Citizen asserted that the revised Declaration meant that 'researchers [would now] have no choice but to provide scientifically proven interventions-regardless of where the research is conducted' (see letter to the editor, **Washington Post**, 17 October 2000).

with professional care. Whilst a physician can combine medical research with clinical care (see Box 5.2), this is only justified by the potential benefits which may accrue for the patient and the group to which he or she belongs and subject to special provisions, including an assessment of the benefits, hazards and discomforts of the new procedure along with a comparison with the advantages of the best current methods, if such exist.[3]

5.11 The Declaration states that the hazards attendant upon the project must be predictable and where they outweigh the potential benefits, the research should not proceed. In carrying out such an assessment, the interests of the subject must always prevail over the interests of science, industry, or society. Furthermore, the Declaration states that participants always have the right to safeguard their integrity and their privacy. The importance of these considerations is that they lead on to the central requirement: that before research related to healthcare can be carried out involving human participants, the participants must first be adequately informed about all relevant aspects of the study including its aims, procedures, attendant risks and hazards and the potential

3 World Medical Association (2000) **Declaration of Helsinki**: paragraphs 28–29 (see Appendix 1).

benefits and discomforts, and then their consent sought. Informed consent must be freely given by the participants. The issue of consent is discussed in Chapter 6.

5.12 As noted in Chapter 1, there has been a major debate over whether the standard of care provided to participants in one specific form of research, the clinical trial,[4] in a developing country should always involve that diagnostic, prophylactic or therapeutic method which has been proved to be the best. Such methods may be beyond the means of those in the developing country. In such a case, it has been argued that it is acceptable to conduct research on new treatments by comparing them with alternative treatments or placebo rather than the best treatment. The current revision of the Declaration states that 'The benefits, risks, burdens and effectiveness of a new method [of treatment] should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods' (paragraph 29). This does not, of course, exclude the use of placebo, or of no treatment, in studies where no proven prophylactic, diagnostic or therapeutic methods exists. But, it appears to stipulate that the best treatment be made available by way of comparison to all other circumstances. Following concerns that paragraph 29 could not be implemented in developing countries, the World Medical Association published a 'clarification note' in 2001. The note states that in general placebo-controlled trials should only be used in the absence of existing, proven therapy. However two exceptions are outlined:

- where for compelling and scientifically sound methodological reasons [the use of placebo-controlled trials] 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 patients who receive placebo will not be subject to any addtional risk of serious or irreversible harm (see Appendix 1).

This issue is discussed in depth in Chapter 7.

5.13 The question of what care a participant should receive once research (combined with medical care) is over has also proved controversial. Guidance on this point was included in the current version (2000) of the Declaration of Helsinki for the first time. Paragraph 19 of the Declaration states that 'Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.' Paragraph 30 states that 'At the conclusion of the study, every patient entered into the study should be

BOX 5.2 Distinguishing between therapeutic and non-therapeutic research

The practice of distinguishing between therapeutic and non-therapeutic research[1] has now largely been abandoned because of a growing recognition that most trials involving therapeutic research contain non-therapeutic components and we have therefore not attempted to make such a distinction in the Report.[2] In the following chapters, much of the discussion focuses on research that contains a therapeutic component (see especially Chapters 7 and 9). However, the discussion of principles underlying research, and in some cases the conclusions and recommendations (particularly in Chapters 6 and 8) are also relevant to research without a therapeutic component.

1 We use the term 'therapeutic research' to indicate research having the potential to produce a real and direct benefit for the participants and 'non-therapeutic research' to mean research without such potential.

2 Nuffield Council on Bioethics (1999) **The ethics of clinical research in developing countries**, Nuffield Council on Bioethics, London.

4 See the glossary for a definition of clinical research and clinical trials.

assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.' We give detailed consideration to this issue in Chapter 9.

The CIOMS guidelines

5.14 CIOMS, in collaboration with WHO, recognised the special circumstances which arise when applying the Declaration of Helsinki to research undertaken in developing countries, and proposed guidelines to address them in 1982. These guidelines sought to direct the conduct of research involving human participants in a way that would recognise the social, economic, legal, regulatory and administrative arrangements that exist in developing nations. They have been widely adopted throughout the world. However, with the increasingly transnational nature of research, and the growing incidence of research involving large-scale clinical trials of medicines and vaccines, particularly following the emergence of HIV and AIDS, further revisions are under consideration.

5.15 In producing revisions, CIOMS/WHO also took into account the growing importance of epidemiological research for public health. In 1991 the **International Guidelines for Ethical Review of Epidemiological Studies** were published. These in turn informed the revised WHO/CIOMS guidance published in 1993 entitled **International Ethical Guidelines for Biomedical Research Involving Human Subjects**. Primacy was given to the protection of the rights and welfare of participants in research, and particularly those considered to be vulnerable. This guidance is currently being modified and the revised edition is expected to be published in 2002.

Other international guidance

5.16 Two further sources of guidance are routinely consulted with regard to the ethical conduct of research. Both draw on the Declaration of Helsinki. First, the **Guidance on Good Clinical Practice**[5] provides unified technical standards for clinical trials so that clinical data generated are mutually acceptable to regulatory authorities in the EU, the US and Japan. Secondly, the **Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products**[6] from WHO lay down basic requirements for the ethical conduct of research. In addition, guidance entitled **Ethical Considerations in HIV Preventive Vaccine Research**[7] was published in 2000 by UNAIDS. Although designed for, and applied in the context of the development of vaccines, the guidance could be of relevance more generally.

National guidance for the conduct of research

5.17 The ethical principles outlined in Chapter 4 have been widely adopted at the national as well as the international level by those developed and developing countries which have established guidance to cover research involving human participants in their own territory. Guidance adopted

5 International Conference on Harmonisation (ICH) (1996) **Harmonised Tripartite Guideline. Guideline on Good Clinical Practice**.
6 World Health Organization (WHO) (1995) **Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products**.
7 UNAIDS (2000) **Ethical Considerations in HIV Preventive Vaccine Research. UNAIDS Guidance Document**, UNAIDS, Geneva.

in Denmark and Uganda is shown in Box 5.3. Some national guidance has the force of law, whilst other guidance is enforced by funding agencies for research as a condition of making a grant, or is simply voluntary codes of practice drawn up by national professional bodies, having persuasive force only. In most cases, the guidance applies within the country or its territories. In some cases, there are specific provisions relating to particular indigenous populations.[8] In New Zealand the importance of ensuring that research related to healthcare contributes to health development in Maori communities has been recognised.[9] Similarly, in Australia the National Health and Medical Research Council (NHMRC) has addressed the ethical issues that arise in connection with research related to health in Aboriginal and Torres Strait Islanders.[10] In other cases, there is specific recognition of the need to take differences in language and culture into account, for example, in the context of obtaining consent.[11]

BOX 5.3 Examples of national guidance: Denmark and Uganda

Denmark has published two laws on the ethics of research related to healthcare involving human participants.[1] These lay down the ethical principles to be considered by a national system of regionally-based committees carrying out review of the ethics of research with a majority of lay members. Since being established in 1980, all projects on healthcare in developing countries involving Danish scientists or Danish public funds have been evaluated under this system, and by the research ethics committees in the host country.

In 1997, **Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda** were published.[2] These were the outcome of a process which began in 1994 to examine Ugandan guidance for the review of scientific research proposals involving human participants. The Guidelines set out general provisions for the protection of participants, along with requirements for institutional review committees, informed consent (including additional protections pertaining to vulnerable populations), and for monitoring and publishing research.

1 Act no. 503 of 1992 and Act no. 499 of 1997.
2 National Consensus Conference on Bioethics and Health Research in Uganda (National Consensus Conference) (1997) **Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda**, National Consensus Conference, Kampala, Uganda.

5.18 In a few cases guidance is explicitly applicable to research carried out under the auspices of national agencies in other geographical areas.[12] For example the US National Institutes of Health (NIH) **Guidelines for the Conduct of Research Involving Human Subjects at the NIH**[13] have been made explicitly applicable to research sponsored from within the US but carried out elsewhere.

8 For example, the National Health and Medical Research Council of Australia (NHMRC) (1999) **National Statement on Ethical Conduct in Research Involving Humans**.
9 The guidelines also emphasise the value of research partnerships between researchers and Maori communities on issues important to Maori health and the importance of encouraging them. To achieve these objectives, in 1998 the Maori Health Committee (MHC) of the Health Research Council of New Zealand published 'Guidelines for Researchers on Health Research involving Maori'. These were based on provisions laid down in the 19th century in the Treaty of Waitangi between the New Zealand government and Maori people. They place considerable emphasis on consultation with the Maori community to ensure that researchers did not offend cultural and tribal sensitivities in the course of research projects.
10 NHMRC published 'Guidelines on Ethical Matters in Aboriginal and Torres Strait Islander Health Research' in 1991. These are directed at the Institutional Ethics Committees (IECs) in Aboriginal and Torres Straits Islander-controlled organisations which deal with ethical approval of project proposals from researchers in these organisations. As with the New Zealand guidelines, these emphasise the importance of consultation with the community-controlled health services and consent of the community for the research.
11 See the Brazilian 'Resolutions 196/1996, 251/1997 and 292/1999'.
12 See, for example, the US NIH (1995) **Guidelines for the Conduct of Research Involving Human Subjects at the National Institutes of Health**, and, in the case of the use of US Federal agency funds **Code of Federal Regulations Title 45 Public Welfare – Part 46 – Protection of Human Subjects** (1991).
13 US NIH (1995) **Guidelines for the Conduct of Research Involving Human Subjects at the National Institutes of Health**.

5.19 In the US, the ethical issues which arise when clinical research sponsored by the US is undertaken overseas were given detailed consideration in the US National Bioethics Advisory Commission's (NBAC) report entitled **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries (2001)**. The Commission expressly discussed the problems that may arise when clinical research that is subject to US guidance is undertaken in developing countries. The report points out that this form of collaboration in research, although desirable, may cause controversy, particularly about the nature of the collaboration and the distribution of any resulting benefits. It also draws attention to the fact that 'Such controversies are perhaps more likely to occur when the nations involved do not share the same cultural, economic, political, and ethical perspectives, or when they are at different stages of development'.[14]

5.20 The NBAC Report emphasises the ethical and logistical problems that arise where research related to healthcare in developing countries is externally sponsored. The studies in question might simply be one way of helping the host country to address a problem in public health, or they might reflect an assessment by a research sponsor that the foreign location is a more convenient, efficient, or less problematic site for conducting a particular study or clinical trial. They might also represent a joint effort to address an important concern for healthcare faced by both parties'.[15] The NBAC Report draws attention to a more fundamental question regarding collaboration in research, particularly that which involves studies in the developing world: whether the existing rules drawn up by the US to regulate researchers working in the US are 'appropriate in the context of international research, or whether they unnecessarily complicate or frustrate otherwise worthy and ethically sound research projects'.[16]

The enforcement of guidance

5.21 As discussed earlier in the Chapter, most of the existing guidance on research related to healthcare does not have the force of law. However, the US Policy for the Protection of Human Subjects, which was inspired by the Belmont Report,[17] has legal force by being incorporated into the US Code of Federal Regulations. A few other countries, such as Denmark, have enshrined the main ethical principles governing medical research in law (see Box 5.3). Other guidance, such as the Council of Europe's **Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine**[18] (Table 5.1) mentioned above, derive their authority through treaty obligations imposed on signatory nations.

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14 National Bioethics Advisory Commission (NBAC) (2001) **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Volume I: Report and Recommendations of the National Bioethics Advisory Commission**: p. 1.

15 NBAC (2001) **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Volume I: Report and Recommendations of the National Bioethics Advisory Commission**: p. 1.

16 NBAC (2001) **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Volume I: Report and Recommendations of the National Bioethics Advisory Commission**: p. 1.

17 The US National Research Act (1974) established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the Commission's charges was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioural research involving human subjects and to develop guidance to ensure research is conducted in accordance with these principles. The Belmont Report represented a summary of the basic ethical principles identified by the Commission in the course of its deliberations, see The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1979) **The Belmont Report. Ethical Principles and Guidelines for the Protection of Human Subjects of Research**, Department of Health, Education, and Welfare, Washington, DC.

18 The Convention, which was adopted in 1997 to bring about the harmonisation of the standards in use within different European countries which have ratified the Convention, goes beyond the issues surrounding research on human participants and deals with a much wider range of medical practices, including issues that will arise out of genomics research and the clinical application of genetics and individuals' access to treatment. The Convention recognises, for instance, that standards are to be applied within local contexts and circumstances. A working party of the Council of Europe has recently prepared a detailed draft additional protocol on biomedical research that will be legally binding on all signatories within European States after its launch. In June 2002, the Steering Committee on Bioethics will review the Protocol. If agreed, it will then be submitted to the Parliamentary Assembly for consultation prior to submission for final adoption by the Committee of Ministers.

5.22 Most of the existing guidance, however, has merely persuasive force and is only enforceable through sanctions imposed on members of the profession or group which was responsible for the particular guidance. The Declaration of Helsinki, produced by the WMA, only binds physicians. Similarly, the CIOMS guidelines only bind members of the signatory organisations. Many involved in research related to healthcare today, however, are not members of the medical profession and thus may not be accountable under these guidelines.

5.23 In other cases, guidance can be enforced by the application of sanctions which will directly affect researchers who do not observe the operating standards and principles laid down. Guidance published by grant-giving agencies, for example, derives its authority from the fact that, unless it is adhered to, financial support for research will be withdrawn or not awarded. Pharmaceutical companies which contravene the guidance contained in the ICH's **Technical Requirements for Registration of Pharmaceuticals for Human Use** will find it difficult, if not impossible, to get a new medicine accepted by the regulatory authorities responsible for issuing licences to market products.

5.24 It is one thing to have guidance, it is another to interpret and apply it. Guidance is liable to different interpretations in different contexts. Furthermore, it is in the nature of such guidance that it does not seek to be comprehensive, given the increasing range of contexts that it is required to cover. For guidance to have the force of law, where it currently does not, a different approach would have to be adopted. The language would have to be clear and relevant to and applicable in a range of contexts and situations. To date this has not been achieved, as was highlighted in many of the responses to the consultation exercise carried out by the Working Party (Appendix 5). It may in fact be difficult to achieve given political and social pressures which come into play when, as a first step, attempts are made to harmonise and clarify the various elements of guidance. Meanwhile, whether or not guidance should have the force of law, there are obviously gaps in existing forms of guidance.

5.25 We have already emphasised that the external sponsors have a duty not to exploit the vulnerable when undertaking research related to healthcare in developing countries. The main aim of the guidance described in this chapter is to protect participants in research from harm, and particularly in the case of developing countries, from exploitation. In practice, researchers and sponsors are often confronted with guidance which is often generalised and even contradictory. Nor does the guidance generally take into account the special circumstances which characterise externally-sponsored research in developing countries. How best then can these countries protect their interests? We suggest two approaches that could be followed in which both developed and developing counties have a role. First, education and training can be arranged to develop expertise in developing countries for the purpose of active participation in the review of the ethics of externally-sponsored research. Secondly, the development of national guidance for the protection of participants in research offers developing countries the opportunity to set their own standards of protection in the light of international guidance. We consider each of these two approaches in turn.

Training

5.26 Guidance on the ethical conduct of research related to healthcare will be of little real value unless it can be understood and applied by sponsors of research, researchers and members of research ethics committees. Provision must be made for the education and training of those involved in research related to healthcare to ensure that guidance on ethical conduct is clearly understood and implemented. We strongly urge that such education and training should be made available not only to researchers and others in developing countries, but also to researchers in developed

countries so that a common understanding is established. **We conclude that in any revised or new guidance the provision of training in the ethical conduct of research should be a requirement placed on all involved in the sponsorship of research in developing countries.**

5.27 Research related to healthcare is not conducted exclusively by medically qualified practitioners. On the contrary, much research in this area is now necessarily multi-disciplinary. Researchers may be biochemists, molecular and cellular biologists, geneticists, psychologists, sociologists, anthropologists or others. All of these should be brought within the ambit of the guidance on ethics that address responsibilities to research participants. **We recommend that national and international sponsors of research ensure that provision is made for education and training in the ethics of research of all of those professionals involved in research related to healthcare to ensure that the requirements of relevant guidance on ethics are met.**

The development of national guidance

5.28 As we noted above, researchers, sponsors and others who are involved in research related to healthcare are faced with diverse and sometime conflicting guidance. A number of developing countries (and many developed countries) have responded to this difficulty by developing their own national guidance to provide a framework for the review of the ethics of research related to healthcare in their countries. Such guidance, which should be based on an interpretation of the international guidance set out in this chapter, generally applies to both externally-sponsored research and internally-funded research. Developing countries which have taken this step include South Africa, Uganda, Nepal, Thailand, India, and Brazil (Appendix 1, Table 1). The development of expertise to formulate national guidance may also require education and training. **We encourage developing countries to take account of existing international and national guidance and to create national guidance for its clear and unambiguous application.** We take the view that, taken together, the development of national guidance and the strengthening of the process of review of the ethics of research related to healthcare will afford a further layer of protection to participants in externally-sponsored research studies and should be priorities for developing countries and sponsors of research.