The ethics of research related to healthcare in developing countries
The terms of reference are as follows:

1. to identify and define ethical questions raised by recent advances in biological and medical research in order to respond to, and to anticipate, public concern;

2. to make arrangements for examining and reporting on such questions with a view to promoting public understanding and discussion; this may lead, where needed, to the formulation of new guidelines by the appropriate regulatory or other body;

3. in the light of the outcome of its work, to publish reports; and to make representations, as the Council may judge appropriate.
Preface

Any report which is concerned with the way in which research related to human health is conducted will be relevant to a wide range of audiences. This Report, the main objective of which is to consider externally-sponsored research as it affects those in developing countries, is particularly broad in its scope. The Working Party met for almost two years and was sustained by a passionate concern for people who take part in research studies in the developing world. This was coupled with the complementary wish to see research into disease and illness being undertaken to the highest standards for the benefit of future generations of patients and for the improvement of the health of populations.

Early on the context of the Working Party’s deliberations was defined. Fulfilling the moral duties of justice and respect in the face of poverty, a lack of resources and the potential for exploitation, presents distinctive challenges to sponsors. We recognised that many of these concern broader issues of public health, of governance and of a lack of facilities, funding and expertise in some parts of the world. Much of this we could do nothing about, other than express our concerns. However we could, within our remit, strongly advocate that appropriate safeguards, based on the ethical principles we identified, be put in place to protect those who take part in research studies.

Research related to healthcare has been hotly debated in recent years, and has been the subject of several reports and investigations. Our contribution should thus be seen as part of that debate and one which focuses on externally-sponsored research conducted in developing countries. We have consulted widely and made a number of fact-finding visits across the world. The Working Party itself was multinational and we reminded ourselves on a regular basis that there were many different ways of considering an ethical issue. Cultural, social and religious differences were part of the context within which we worked. We have therefore considered the issues from the point of view of a population or of a research participant who is being studied in a particular context. We hope that this will ensure that the breadth of our thinking will assist in the recommendations being taken forward.

The recommendations are relevant to a wide range of organisations, agencies and national governments, as well as to research participants themselves. They concern issues of consent, standards of care, ethical review, and what should be done once the research is completed. We hope that they will be widely debated and taken up. We intend to review the response to the Report in 18 months’ time.

I should like to thank the members of the group for their hard work and enthusiasm, we worked well as a team. I would particularly like to thank the Director of the Nuffield Council on Bioethics, Dr Sandy Thomas for all her input into the work of the group and for keeping us on the straight and narrow. To Julia Fox, Yvonne Melia and Tor Lezemore for all they contributed. Special thanks however must go to Susan Bull, whose tireless work and good humour helped us to get to the end of the Report with style and with a sense of achievement. It has been a privilege to chair the Working Party and I hope that the Report will stimulate the discussion and debate which the issues deserve.

Kenneth C Calman.
Acknowledgements

The Working Party wishes to thank the many organisations and individuals who have assisted its work, particularly those who attended fact-finding meetings or submitted consultation responses. It would also like to thank those who responded to the Working Party’s requests for advice on specific areas of the Report. In addition the Working Party is very grateful to Dr Vichai Chokevivat, Dr Soledad Diaz, Professor Sir Colin Dollery, Dame Rennie Fritchie DBE, Professor Helen Lambert, Professor Adetokunbo Lucas, Professor Ruth Macklin, Dr Vasantha Muthuswamy and Baroness Onora O’Neill, who all reviewed an earlier version of the Report. Their comments, which contained both far-reaching and detailed criticisms to which we have sought to respond, were extremely helpful.
The ethics of research related to healthcare in developing countries

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The ethics of research related to healthcare in developing countries

Terms of reference

1. To review the importance of healthcare-related research in humans, supported by those in more affluent countries and conducted, at least partly, in developing countries.

2. To identify and consider the ethical and social implications of conducting such research including:
   (a) who benefits from the research;
   (b) consent;
   (c) differences in cultural values;
   (d) differences in levels of healthcare between countries;
   (e) compatibility of ethical guidelines produced by international bodies;
   (f) the respective responsibilities of local and non-local ethics review bodies, and mechanisms for review and monitoring;
   (g) follow-up, including the possible implementation of findings, after the completion of research.

3. To make recommendations.
Executive summary

The purpose of this Report is to examine the ethical issues raised when research related to healthcare is carried out in developing countries and funded by sponsors from developed countries. Developing countries urgently need research to help to address the enormous burden of disease that they carry. The inequalities in resources between developed and developing countries pose a real risk of exploitation in the context of externally-sponsored research. Recognising that external sponsors differ in their motives for conducting research in developing countries, the Working Party considers that all countries should set national priorities related to their provision of healthcare. When externally-sponsored research is proposed which falls outside the national priorities, its relevance must be justified to the appropriate research ethics committees. To enhance the ability of developing countries to conduct research that is relevant to their needs, the Working Party recommends that the development of local expertise in the provision of healthcare and in healthcare research should be an integral component of any proposed research.

The Working Party recognises that those involved in externally-sponsored research are often faced with diverse and sometimes conflicting guidance as to what may be ethically acceptable. This Report aims to present an ethical framework for others to use when applying such guidance and to assist those involved in the development of national guidance for the ethical review of research. The ethical framework proposed in this Report is based on four principles: 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. It is crucial that these duties are respected when research is planned and conducted. The Working Party emphasises the critical importance of taking into account the context, social, cultural and economic, when applying these principles. Further, it identifies certain minimum requirements that must be met.

Consent

The Working Party concludes that in some cultural contexts it may be appropriate to obtain agreement from the particular community or assent from a senior family member, before any prospective participant in research is approached. However, genuine consent to participate in research must also always be obtained from each participant.

Standards of care

The Working Party concludes that the appropriate standard of care to be provided to members of a control group in a research project can only be defined in consultation with those who work within the country in which the research is to be conducted. It must then be justified to the relevant research ethics committees. Wherever appropriate, participants in the control group should be offered a universal standard of care1 for the disease being studied. Where it is inappropriate to offer such a standard, the minimum that should be offered is the best intervention currently available as part of the national public health system.

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1 We use the term ‘universal standard of care’ to indicate the best current method of treatment available anywhere in the world for a particular disease or condition.
Once a research project is completed

The Working Party concludes that it is unacceptable for research to begin without a decision having been made about whether or not participants in the control group will be offered an intervention shown to be successful on completion of the trial. Researchers should endeavour to secure post-trial access to effective interventions for all the participants in a trial who could benefit. In addition, the possibility of introducing and maintaining a successful treatment in the wider community should be considered before research is conducted. If it is thought that this will not be possible, researchers must justify to the relevant research ethics committee why the research should be carried out.

Reviewing the ethics of a research project

An effective system of review of the ethical propriety of research is a crucial safeguard for participants in research. It may, however, be absent or ineffective in some developing countries. The Working Party recommends that all countries should establish an effective system for the ethical review of research, which includes the establishment and maintenance of research ethics committees that are independent of government and sponsors of research. Research should be subject to ethical review in both the country(ies) hosting and the country(ies) sponsoring the research. The Working Party welcomes international initiatives for establishing research ethics committees, training their members and monitoring their development. Funding should be provided for these purposes by those who sponsor research in developing countries. Furthermore, the Working Party recommends that national and international sponsors of research should ensure that adequate provision is made for training of all those professionals involved in research related to healthcare in the ethics of research.
Chapter 10

Conclusions and recommendations
Introduction

10.1 Many people in developing countries suffer from poor health and reduced life expectancy. Poverty, coupled with limited scientific, administrative and political development often makes it very difficult for developing countries to improve healthcare. Those who seek to improve the health status of developing countries do so against this background, in which poor health is a reflection of the larger inequality. We have focused on one aspect of healthcare, that of research. Developing countries urgently need research related to healthcare which addresses their burden of disease. It is therefore axiomatic that externally-sponsored research that seeks to bring health benefits, should, with appropriate safeguards, be encouraged in developing countries. We consider, moreover, that there is virtue in research which provides not only direct benefits to participants such as treatments for specific health needs but also indirect benefits arising from the influx of resources into a local community and the enhancement of expertise in research.

10.2 We ask how the conduct of healthcare research in developing countries, much of which is funded by sponsors in developed countries, can be consistent with principles of justice. Our primary focus is not on the existence of injustice on a global scale but on its implications for those who have the power to act, whether within or outside of developing countries, including governments, research councils, private companies and researchers. The inequalities in resources between external sponsors of research into healthcare, and communities and governmental authorities in the developing countries, will often be so great that there is a real risk of exploitation in the context of externally-sponsored research. It is crucial therefore that the four principles which form the ethical framework for this Report: 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 are respected when research is planned and that appropriate safeguards are put in place.

10.3 The Working Party has made a number of recommendations to guide external sponsors of research related to healthcare. While these recommendations are, for the most part, directed to external sponsors, this is not to suggest that the principles on which they are based are not equally applicable to internally funded, national research. The recommendations, taken together, should be regarded as a framework for the ethical conduct of research, whoever the sponsor might be.

10.4 Our central aim has been to consider how individuals and organisations from developed countries should conduct themselves when sponsoring or undertaking research related to healthcare in developing countries. We have examined the ethical issues raised by externally-sponsored research and considered ways in which they might be resolved. The disparity between the resources and power of the external sponsor of research and the developing country has been central to the discussion. We recognise that external sponsors, whether they be multinational pharmaceutical companies or publicly funded research organisations, may differ in their motives for undertaking research related to healthcare in developing countries. Despite these differences, we consider that all externally-sponsored research should be required to fall within the ambit of the national priorities for research related to healthcare within developing countries, unless the reason for not doing so can be justified to the appropriate research ethics committee within that country. Not only must the people who are part of that research be treated with respect, but the balance between the interests of these individuals and the interests of the wider community from which they are drawn must be carefully weighed.

10.5 When planning and conducting research, researchers and their sponsors have a duty to recognise the importance of national and local cultures and social systems, values and beliefs. In addition, external sponsors have an obligation to educate and train members of the local and national communities in the methods and skills of conducting research. The need for research projects to
be subjected to review as to their ethical propriety is paramount. There is an urgent need for further education and training to ensure that those in developing countries are able to discuss ethical issues effectively with external sponsors and others and to have mechanisms in place to deal with issues that arise. Most importantly, research ethics committees in developing countries have the responsibility of sanctioning only that research which is appropriate and of challenging and preventing research that is not.

10.6 The four main topics of our Report – standards of care, consent, the ethical review of research, and what happens when the research is over – emerged as we examined the subject in detail and in response to questions raised during our deliberations. Some of the recommendations which we make on these topics have been directed to particular agencies with a view to their taking them forward. We also set out an agenda for action by those in developing countries so as to develop expertise in the conduct of research and effective procedures for the ethical review of research proposals.

Healthcare economics

10.7 The major inequalities in health which exist across the world are closely related to levels of social and economic development. The burden of disease in the majority of developing countries is enormous. The active participation of many agencies will be required if change is to be achieved. Research on new forms of interventions and on more effective ways of delivering new or existing interventions is crucial. The cost of the process of evaluating a new intervention through clinical research can be very high; so high that it could not be covered by many developing countries without external support. In addition, many forms of interventions, especially new medicines and vaccines, may be very costly to manufacture or purchase. However, there are examples which show that, once an intervention, such as a medicine or a vaccine, has been shown to be effective, ways may be found of substantially reducing the costs of providing such an intervention to a developing country. Despite the great need for research to determine which forms of intervention in developing countries are most effective, the capacity of those countries to conduct relevant research is severely limited. Developing expertise in research to help countries to set their own priorities and to focus research on those priorities is a crucial obligation that sponsors of externally-funded research must acknowledge.

Setting priorities for research

10.8 Setting priorities for healthcare research is a particularly important issue in developing countries, because national resources for research are generally very limited. Clearly, 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. If there is no clear picture of the priorities for research related to healthcare within a country, it will be more difficult for government and external sponsors to collaborate in addressing them.

10.9 It follows that to enable effective collaboration with external sponsors, developing countries should have a mechanism allowing them to set priorities for research into healthcare, together with a robust mechanism for scientific review and ethical review of any proposed research (see Chapter 8). How this is managed will depend on the resources available in each country. We therefore endorse the view of the Commission on Health Research for Development (1990) and its successor, the Task Force on Health Research for Development (1991) that all countries should set priorities for research into healthcare (paragraph 2.31).
Failure to do so may mean that external sponsors wishing to conduct research will be unable to identify a country’s crucial needs as regards research into healthcare and therefore may be more likely to propose inappropriate research with little relevance to the country in which it is conducted.

10.10 We do not take the view that all externally-sponsored research should fall within nationally defined priorities, since all research has the potential to contribute to the development of local skills and expertise, quite apart from the inherent value in diversity of research. However, there is a careful balance to be drawn. The inherent inequalities of power and advantage between developed and developing countries require that particular care is needed to restrain any tendency on the part of the sponsor to pursue their interests to the detriment of those of the host country. **We therefore recommend that when research funded by external sponsors is proposed which falls outside the national priorities for research into healthcare set by a host country, those proposing the research be required to justify the choice of the research topic to the appropriate research ethics committees in both the host and sponsoring countries (paragraph 2.32).**

### Social and cultural issues

10.11 Systems of biomedical care in developed countries are generally based on common scientific assumptions. There are, however, a variety of other systems of diagnosis and healing which may vary a great deal across cultures and countries. This is particularly true of developing countries. Research into healthcare conducted along scientific lines in a particular society, or culture, will be affected by existing assumptions and practices. In any research in developing countries, therefore, these need to be addressed. Particular attention will need to be given to the means of informing potential participants about the proposed study and the process of seeking their consent. The differing conceptions of what respect for persons entails in many societies in the developing world, and the need for the community to discuss issues and reach agreement as a first step in the approval of a research project must be taken into account by researchers.

10.12 Research which pays no regard to the development of local infrastructures, or which fails to make appropriate use of local systems, skills and practitioners, may fail to maximise the benefit of the research to the community. The possibility and desirability of co-operation between practitioners of traditional medicines and scientific researchers on a particular research project should be considered on a case-by-case basis.

### Ethical principles

10.13 The Working Party identified four ethical duties that are crucial in evaluating the actions and policies of individuals and organisations proposing to carry out research in developing countries. The four duties are the duty to alleviate suffering, to show respect for persons, to be sensitive to cultural differences, and the duty not to exploit the vulnerable. They constitute a framework for articulating the duties, obligations, claims and expectations of those involved in research related to healthcare. The practice of medicine is intrinsically justified by virtue of the duty to alleviate suffering. Research into healthcare makes an essential contribution to the alleviation of suffering. While the needs of our own communities may generally have the first claim on our resources, we have a duty to contribute to the alleviation of suffering elsewhere. Thus, there is an ethical imperative to conduct research, including that which addresses the health problems of developing countries.

10.14 The principle of respect for persons places important constraints on the performance of the duty to alleviate suffering. That duty, by itself, may lead us to the assumption that the less
suffering there is, the better the world is overall. However, the principle of respect for persons enjoins us to consider carefully the ways in which we seek to alleviate suffering. For example, policies which violate other interests of those involved, even if they offer the most straightforward way of reducing suffering, are to be weighed carefully.

10.15 An important characteristic of externally-sponsored research conducted in developing countries is that there are often cultural differences between those organising or funding the research and the researchers and participants in the host country. One potentially potent misuse of power is to be insensitive to the cultural perspectives that individuals bring to questions of health and healthcare. Indeed, the variety of beliefs and practices that exist may challenge the notions of overarching ethical principles. It may be claimed that the requirement to practice sensitivity to cultural differences leads to moral relativism, which is the view that different moral codes cannot be critically compared and evaluated. In our view, the existence of cultural diversity does not lead to moral relativism. Sensitivity to the values inherent in local practices does not require uncritical acceptance of them. What is required is a willingness to explore differences without prejudice and to seek as far as possible to understand them, informed by knowledge of local traditions and material circumstances.

10.16 We suggest that, as a matter of moral principle, the more powerful have a duty to refrain from exploiting to their own advantage the vulnerability of the weaker. Just as it is unacceptable that local political and economic elites should seek to pursue their own goals at the expense of populations participating in research, so it is unacceptable that researchers should select populations which are economically or politically weak and therefore vulnerable to exploitation, in order to test therapies more cheaply or in order to use the results for the benefit of other, more wealthy, communities.

The framework of guidance

10.17 The Working Party noted that an ethical inquiry does not concern itself only with the articulation of appropriate general values and principles; it has also to concern itself with the institutions and procedures through which these principles are put into practice. Researchers and sponsors who undertake research related to healthcare in developing countries are faced with difficult choices. On the one hand, they need to be sensitive to the local social and cultural context, while on the other they need to ensure that their clinical methods reflect the obligations imposed by the relevant national and international guidance. In practice, researchers and sponsors have been confronted with guidance which is often generalised and even contradictory. Nor has the guidance generally taken into account the special circumstances which characterise externally-sponsored research in developing countries.

10.18 The Working Party has concluded that training in interpreting and applying the guidance is an important accompaniment to the guidance itself. Unless guidance is clearly understood by researchers, sponsors and the members of the research ethics committees, it will be of little real value. So that a common understanding is established between researchers in both developing and developed countries, we suggest that education and training of those involved in biomedical research is undertaken so that the requirements of the guidance are clearly understood and implemented. 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 (paragraph 5.26). We recommend that national and international sponsors of research, including government agencies and departments, charitable foundations and pharmaceutical companies, 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 (paragraph 5.27). In addition, we encourage developing countries to take account of existing international and national guidance and to create national guidance for its clear and unambiguous application (paragraph 5.28).

**Consent**

10.19 The fundamental ethical duty of respect for persons requires that we do not act against a person’s wishes, and thus genuine consent to participate in research must be obtained. For consent to be genuine, 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. It must include such matters as the nature and purpose of the research, the procedures involved and the potential risks and benefits.

10.20 An awareness of the social and cultural context in which research is to be conducted is required, so that communities and individuals can be informed of any aspect of the research that may cause them particular concern. The process of obtaining consent also needs to be designed to provide opportunities for participants to ask questions of personal interest about the proposed research.

10.21 In some circumstances there is a tension between the requirement that genuine consent to research be obtained, and cultural contexts in which giving certain information, such as a diagnosis of a serious disease to a patient, is not customary. The Working Party has considered these competing interests and has concluded that obtaining genuine consent to research from participants is vital in ensuring that respect for persons is promoted. Without appropriate information, participants in research may be harmed by being exposed to risks or dangers that they would prefer to avoid. In addition, they will be denied the opportunity to learn more about their condition, possible treatments, and any beneficial outcomes of the research. Consequently, when research is conducted in contexts in which information about diagnoses and options for treatment is not normally provided, care and sensitivity will be required to design appropriate consent procedures, so that participants receive appropriate information about research and genuine consent may be given.

10.22 For consent to be genuine, it must be freely given. In some societies it would be considered culturally inappropriate for researchers to ask individuals to participate in research without consulting the community or permission from community leaders. Three such situations can be distinguished: consultation is required with the community before individuals are approached about research; permission from a leader(s) of the community is required before any research is discussed with the community or individuals; the leader of the community is considered to have the authority to enrol participants in research. In each of these circumstances, to seek consent from an individual without seeking assent from leader(s) of the community, or creating public acceptance of research, may be considered disrespectful and may harm relationships within that community and between a community and researchers. We noted in Chapter 4 that we cannot avoid the responsibility of taking a view when the two aspects of respect – respect for culture and respect for persons – come into conflict with one another. We are of the view that the fundamental principle of respect for persons requires that participants who have the capacity to consent to research should never be subjected to research without such consent. The Working Party has concluded that assent from others may be necessary before research is conducted, but that it is not sufficient: individual participants must receive appropriate information about the research and be asked to give consent. To ensure that individual participants can make up their
own minds without undue communal pressure, anonymity for those who wish to decline to participate in research should be assured. **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. Researchers must not enrol such individuals and have a duty to facilitate their non-participation (paragraph 6.22).**

10.23 Participants in research may have a variety of motivations for taking part in research. The healthcare that a participant would receive as part of a research programme may amount to a significant inducement to take part. Researchers will need to be aware that when research is conducted in developing counties, prospective participants may have little or no alternative means of receiving healthcare for a condition, other than through the facilities supported by the research, and thus the healthcare provided as part of the research will amount to a significant inducement to participate. In addition, benefits unrelated to the research protocol, such as financial payments, may be offered to compensate for travel costs or time devoted to the research. The dividing line between acceptable and inappropriate inducements is a fine one. The larger an inducement, the more likely it is to be inappropriate, because it causes an individual to expose himself or herself to risks or potential harms that he or she would otherwise consider to be unacceptable. In addition, payments and other benefits unrelated to the research protocol will act as significantly greater inducements in developing countries than would similar amounts in more developed contexts. **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).**

10.24 Concerns have been expressed that consent forms and information sheets used for research in developing countries may contain terms that are commonly used in the countries of those sponsoring the research but are inappropriate in the context in which the research is being conducted. Various forms of guidance give detailed indications of the matters about which participants should be informed.¹ It should always be remembered that such devices as information sheets and consent forms are intended to assist the consent process. Researchers will need to refer to the relevant guidance and consider which matters are relevant to their research and to the context in which the research is to be conducted, and how to express the information they seek to convey. Forms which are long, complex and inappropriate for the cultural context in which they are being used, are likely to confuse, rather than inform, participants in research, and should not be approved by research ethics committees.

10.25 There are circumstances in which, while genuine consent to research can be obtained, it may be inappropriate to ask participants in research to sign consent forms, no matter how well designed. One obvious example is when research is being conducted in an illiterate population. The Working Party considers that it is not consistent with the duty of respect for persons to require a prospective participant to ‘sign’ a written consent form that they are unable to read.

¹ For example, Guideline 2 of the CIOMS 1993 International Ethical Guidelines for Biomedical Research Involving Human Subjects specifies 10 pieces of essential information which should be given to prospective research participants, including: the aims and methods of the research, the benefits that might reasonably be expected to result to the research participant or to others as an outcome of the research, any foreseeable risks or discomforts, the extent of the investigator’s responsibility, if any, to provide medical services to the research participant, confidentiality of participant data and arrangements for compensation for research-related injuries.
In such circumstances other means of recording genuine consent to participate is required, to protect participants from being enrolled in research that they have not consented to. **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. 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 (paragraph 6.40).

### Standards of care

10.26 There has been significant international debate about the standards of care that should be provided to participants during externally-sponsored research in developing countries. In this Report, we have focused on the question of whether participants in the control group of a research trial should be provided with a universal standard of care, regardless of where the research is conducted. The different approaches that have been proposed when deciding the level of care that should be provided for those in the control group of a clinical trial can be divided into two broad categories:

- universal: the best treatment available anywhere in the world, wherever the research is conducted
- non-universal: the treatment available in a defined region.

10.27 The Working Party is firmly of the view that the need to avoid exploitation is imperative. It is a fundamental ethical principle that those involved in research should not take advantage of the vulnerabilities created by poverty or a lack of infrastructure and resources. However, the Working Party considers is that insisting upon a universal standard of care may not always be the best way to respect this principle.

10.28 At first sight, justice might seem to require that we treat people identically, regardless of context, because justice demands equal respect. If showing respect for the participants in a particular research project in the developed world demands that they receive a particular intervention, it would seem to follow that participants in similar research conducted in the developing world should receive the same intervention. To apply a lower standard of care would thus be not only to take advantage of the participants’ vulnerabilities, but also to commit an additional wrong by perpetuating an injustice. However, the principle of equal respect does not imply that we must behave towards others in a uniform manner, since features of individuals and of their circumstances will differ. Parity of respect requires us to address the specific needs and circumstances of individuals in determining how to behave towards them. What we mean by equality is not that people must always be treated identically, but that ‘for every difference in the way men are treated, a [relevant] reason should be given’. Thus, equal respect for participants in research does not necessarily entail that they should receive equal treatment, regardless of where the research may be conducted. Instead, the circumstances in which the

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research will be conducted must be critically assessed to establish whether or not the variations in circumstances provide a morally relevant reason for offering a different standard of care.

10.29 We take the view that, in determining the appropriate standard of care to be provided to participants in the control group of a research trial, a number of factors should be considered by sponsors, researchers, and research ethics committees. These include:

- the appropriate research design(s) to answer the research question (in some situations only one research design may be appropriate to answer the research question, in others a number of research designs, in which different standards of care are offered to the control group, may be possible)
- the seriousness of the disease and the effect of proven treatments
- the existence of a universal standard of care for the disease or condition in question and the quality of the supporting evidence
- the standard(s) of care in the host and sponsoring country(ies) for the disease being studied
- the standard(s) of care which can be afforded by the host and sponsoring country(ies) for the disease being studied
- the standard(s) of care which can effectively be delivered in the host country(ies) during research
- the standard(s) of care which can be provided in the host country(ies) on a sustainable basis.

10.30 Taking the above considerations into account, in some circumstances, it will be clear that a control group in a clinical trial should receive a universal standard of care, wherever they live. In contrast, there are situations in which it is clear that even if there were an agreed universal standard of care for a disease, it may not be possible for this standard to be provided to the control group in a research project. This may be because of practical considerations, for example because the country in which the research is to be conducted may not have the infrastructure to provide such treatment, or because research using such a standard of care would have little relevance to the country in which it is conducted. The decision about whether or not a universal standard of care should be provided to the control group is usually not straightforward and involves careful consideration of the factors outlined above.

10.31 Where it is not appropriate to require that a universal standard of care be provided to the control group in the light of all the relevant circumstances, questions arise about what standard of care should be provided. The ultimate goal of research must be to provide information about treatment and other interventions which can then be used by national governments to ensure that improvements are made in the provision of healthcare. Thus, for policy reasons, it seems sensible to take the particular country as the unit of focus, as it is national governments which, by and large, take responsibility for the health of their citizens and which make decisions about the provision of healthcare. With knowledge of the resources available to them, governments make decisions about the level of care which they can provide for the prevention and treatment of specific diseases or conditions. In that context, they set targets for the level of care that they will strive to achieve, often recognising that it will not be possible to meet this goal.

10.32 The Working Party is of the view that in externally-sponsored research, the level of care that ought be offered to participants should, as a minimum, be the standard that the country endeavours to provide nationally. In many circumstances, it may be appropriate for researchers to offer a higher level of care than this, while still conducting research that is relevant to the local setting.
10.33 We conclude that discussion with clinicians, researchers and representatives of government and health authorities within the host country is essential so as to establish what the best national level of treatment available as part of the national public health system is. We recommend that in setting the standard of care for the 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). In research that aims to improve current forms of treatment within a developing country it may be proposed that the standard of care to be provided to the control group is lower than the best available intervention as part of the host country’s public health system. In exceptional circumstances such research may be justified (see paragraphs 7.30–7.31).

10.34 In some forms of research, such as those designed to determine the incidence of a disease in a population, or to prevent participants from contracting or developing a disease, the standard of care received by participants who develop the disease will not be immediately relevant to the research. Under these circumstances, however, there is still a need to consider the standard of care which a patient should receive because the disease, once diagnosed, may have serious implications for the individual. The issue was the subject of extensive consultation when the UNAIDS guidance on ethical considerations in research on a HIV preventive vaccine was drafted. We endorse Guidance Point 16 of the UNAIDS guidance on Ethical Considerations in HIV Preventive Vaccine Research. We conclude that when research into preventive measures is conducted, wherever appropriate, participants who develop the disease being studied should be offered a universal standard of care for the disease under study. Where it is not appropriate to offer a universal standard of care, the minimum standard of care that should be offered is the best available intervention as part of the national public health system for that disease (paragraph 7.33).

10.35 During research into some diseases, participants may develop a condition that is related to the condition under study or an entirely unrelated condition. In some circumstances, it may be relatively easy for researchers to treat the condition or refer participants to a centre where treatment can be provided. In other cases, researchers may not have the expertise to treat the condition effectively and appropriate treatment may not be available locally as part of the public health system. This is a complex issue and decisions will need to be made on a case-by-case basis following discussion with clinicians, researchers and representatives of government and health authorities within the host country. We recommend that before research begins, 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 must be justified to the relevant research ethics committees (paragraph 7.35).

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3 UNAIDS (2000) Ethical Considerations in HIV Preventive Vaccine Research. UNAIDS Guidance Document: Guidance Point 16: Care and treatment for HIV/AIDS and its associated complications should be provided to participants in HIV preventive vaccine trials, with the ideal being to provide the best proven therapy, and the minimum to provide the highest level of care attainable in the host country in light of the circumstances listed below. A comprehensive care package should be agreed upon through a host/community/sponsor dialogue, which reaches consensus prior to initiation of a trial, taking into consideration the following: level of care and treatment available in the sponsor country; highest level of care available in the host country; highest level of treatment available in the host country, including the availability of antiretroviral therapy outside the research context in the host country; availability of infrastructure to provide care and treatment in the context of research; and potential duration and sustainability of care and treatment for the trial participant.
Ethical review of research

10.36 The requirement that the ethics of research related to healthcare is subject to review is designed to protect participants in research. The Working Party considers that each proposal for externally-sponsored research in developing countries should receive three levels of assessment: relevance to priorities in healthcare within the country(ies); scientific validity; and ethical acceptability. While research ethics committees are not constituted to make decisions about whether or not the findings of research can be implemented within a country, they should, however, determine if the implications of possible research results have been discussed, including the possibility of ongoing provision of treatments shown to be successful. Research ethics committees must also be satisfied that appropriate scientific review of research has taken place. We accept that it is not possible to separate entirely the processes of reviewing the science and ethics of a research proposal, but as the two forms of review have quite different purposes we conclude that they should, where possible, be kept separate (paragraph 8.5). This may, but will not necessarily, require the establishment of separate committees.

10.37 We have outlined a number of issues which research ethics committees need to consider when reviewing externally-sponsored research. These include the appropriateness of procedures for giving information about the research to prospective participants and communities and recording consent; the standards of care that should be provided to participants in research and arrangements that have been made for post-trial access to interventions.

10.38 The mere presence of a research ethics committee in a country is not enough to ensure that research will be adequately reviewed. Committees may be ineffective for a variety of reasons, including a lack of financial and human resources, and a lack of training in, and experience of, ethical review. An effective system for ethical review is a crucial safeguard for participants in research. We recommend that 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. 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).

10.39 In developing countries, research ethics committees may have access to only limited administrative or financial support. To meet the costs of effective review, some research ethics committees receive regular funding from government. Others levy fees for reviewing research protocols. Regardless of whether the financial support for research ethics committees comes from government, research institutions or as a result of levying fees for review, it is crucial that the independence of research ethics committees be maintained. 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).

10.40 In order to ensure that acceptable ethical standards are observed in externally-sponsored research, research should be approved through a system of ethical review of research in both the host and the sponsoring country. As regards the latter, if a sponsor provides funding, it must
have the means of ensuring that the funds are being used in a manner that is ethically acceptable. However, the country in which the research is to be conducted must also be satisfied about the ethical acceptability of the research. **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).** Should there be disagreement between committees in the developed and developing country(ies), negotiation between the committees in the sponsor’s country and the country in which the research is to be conducted may be required. There should be mechanisms available to facilitate such negotiation. Where there are irreconcilable differences between research ethics committees, a committee may choose not to approve the research.

10.41 For research ethics committees to function effectively, committee members must receive adequate training. A number of national and international programmes are being established to develop expertise in ethical review in developing countries. Concerns have been expressed that training programmes for members of research ethics committees in developing countries, sponsored by a single developed country, may tend to reflect the views and procedures of the sponsoring country. **We recommend that international programmes and organisations, including the World Health Organization (WHO), continue to expand their current programmes for establishing, training and monitoring the development of research ethics committees.** Funding should be provided to these international programmes for such purposes by bodies that sponsor research in developing countries (paragraph 8.29).

**What happens once research is over?**

10.42 Once an externally-sponsored research study is completed in a developing country, the researchers and their sponsors are confronted with a number of issues relating to the future provision of healthcare benefits to the participants in the research and to the wider community. Many have taken the view that to fail to provide treatment which has been shown to be successful to the participants in research is ethically unacceptable. We take the view that in general, it is the responsibility of governments and not researchers or sponsors to determine the level of healthcare and the range of treatments and medicines that are provided to populations. However, researchers and sponsors often directly contribute to the strengthening of local healthcare facilities, so as to facilitate the research and to act as an inducement to individuals to participate. In addition, researchers may and frequently do act as advocates for the adoption of a medicine or vaccine shown to be successful. We recognise that sponsors are rarely in a position to agree to open-ended commitments once the research is completed, whether for the maintenance of facilities for healthcare or for the provision of interventions, but these are issues that need to be discussed and agreed by the research ethics committee, to the extent possible, before the research is initiated.

10.43 In externally-sponsored research, a valuable contribution can be made towards the development of local expertise during the research, so that there is the potential for continued improvement in healthcare once the research is complete. **We endorse the Council of International Organisations of Medical Sciences (CIOMS) Guidelines (1993) (Guideline 15) and recommend that sponsors of research should require that the development of local expertise in healthcare is an integral component of research proposals. Consideration should be given to the extent to which any strengthening of local healthcare facilities can be done in such a way that the changes are sustainable in the local context once the research is over (paragraph 9.12).**
With regard to the provision of an intervention shown to be successful once the research is completed, there are three groups of people to be considered: members of the control group in a trial, all of the participants in the research project, and the wider community in which the research took place.

The principle that those in the control arm of a trial should be provided with the intervention when it has been demonstrated to be efficacious is widely acknowledged. We consider that there is an ethical obligation to provide a control group with an intervention when it would benefit them (paragraph 9.24). We conclude moreover that it would not be ethically acceptable for any study to begin without a decision having been made about whether or not those in control groups will be offered an intervention shown to be successful on completion of the trial, where relevant and appropriate. Participants should be informed of the decision as part of the process of obtaining their consent (paragraph 9.27).

Participants in research may have conditions that require ongoing treatment. In such cases, it may be suggested that there is an obligation to continue to provide an intervention that has been shown to be effective to all participants. While such a requirement would be commendably aspirational, it may not be possible, especially in relation to ongoing treatment for chronic diseases. We therefore endorse the US National Bioethics Advisory Commission (NBAC) recommendation that researchers should 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).

The most contentious issue concerning the future provision of benefits arising from research related to healthcare is the availability of successful interventions to the wider community once research is over. The Working Party acknowledges that if sponsors were required to fund the future provision of effective interventions, the majority would no longer support such research. Provision of a successful intervention to the wider community is primarily the responsibility of governments. However, there have been significant contributions from the pharmaceutical industry, although these are, by necessity, seldom open-ended. We have concluded that the complexity of the circumstances relating to the availability of interventions after the completion of a trial makes it difficult to formulate general guidance which applies to different forms of interventions. The need for further research, the role for research relating to the local delivery of interventions, the change in the cost of medicines, the existing framework for healthcare, and the commitment of policy-makers, are all factors which will influence the availability of a successful intervention. Despite these uncertainties, we conclude that there is a duty on researchers to address the issue before any research is initiated.

We recommend that the following issues are clearly considered by researchers, sponsors, national healthcare authorities, international agencies and research ethics committees as part of any research protocol before research relating to healthcare involving the testing of new interventions is undertaken:

- the need, where appropriate, to monitor possible long-term deleterious outcomes arising from the research, for an agreed period of time beyond the completion of the research
- the possibility of providing participants with the intervention shown to be best (if they are still able to benefit from it), for an agreed period of time

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• the possibility of introducing and maintaining the availability to the wider community of treatment shown to be successful (paragraph 9.48).  

10.49 We endorse the NBAC recommendation that 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 committee why the research should be carried out if this is not thought possible (paragraph 9.49).

10.50 Despite the very great need for healthcare research in developing countries, local expertise in research tends to be severely limited. It is therefore particularly important that sponsors of research promote genuine partnerships between researchers in developed and developing countries when research is externally sponsored in order to strengthen expertise in research and maximise the opportunity for the transfer of knowledge and skills. We recommend that external sponsors of research should require that the development of expertise in research be an integral component of all research in developing countries. Consideration should also be given to the development and support of expertise so that equipment obtained for the purposes of a research project can continue to be used and maintained (paragraph 9.52).

Concluding comments: a framework for future action

10.51 In this Report, we have set out an ethical framework for assessing the duties and responsibilities of those involved in designing and conducting research related to healthcare. The framework is based on four principles: 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. Rather than formulating a strict prescription of conduct which these principles would require when research in developing countries is externally sponsored (such as stipulating that a universal standard of care be provided), we have emphasised the critical importance of taking social, cultural and economic contexts into account when applying these principles, and have identified the minimum requirements which must be met in all circumstances. Particular care is required in those countries which do not have well established procedures for the protection of participants in research.

10.52 We are aware that researchers, sponsors and others who are involved in research related to healthcare are faced with diverse and sometimes conflicting guidance. Our contribution therefore has been to present an ethical framework as a guide for others to use when determining how to apply the guidance. In particular, the development of national guidance and the strengthening of the process of ethical review of research are priorities for developing countries which will afford a further layer of protection to participants in research.

10.53 In this Report we have argued for approaches to consent, standards of care, ethical review and the future provision of healthcare that take into account not only the need to protect participants in research, but also the economic realities that are faced by the majority of developing countries. In doing this, it is crucial that the recommendations in this Report are taken as a whole. Thus, the flexibility in tailoring standards of care and procedures for obtaining consent for specific research projects must be accompanied by the development of a rigorous and effective process of ethical review that assesses the appropriateness of the proposed research. This will allow research to be designed so that it has the greatest chance of providing relevant information about a population and thus alleviating suffering, without risking exploitation of vulnerable communities.

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5 This consideration is especially important for expensive interventions.