

# Chapter 9

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*What happens once  
research is over?*

## Introduction

- 9.1 Much of the debate about the ethical issues which arise in externally-sponsored research in developing countries has focused on the protection of the participants during the study. However, there are also important issues concerning the welfare of those who have participated in the research and of the wider community once the research is over. The subsequent provision of interventions shown by the research to be successful, and continuing the provision of healthcare to research participants and to the wider community, are complex issues which confront researchers, research sponsors and providers of health services. Uncertainty about whether an experimental intervention will in fact prove to be successful, or be affordable, and the difficulty of guaranteeing that it will be available in the long-term have discouraged research sponsors from making commitments to participants and the wider community prior to embarking on any research. What makes these issues particularly difficult to resolve is that the possibility of introducing an intervention that has been shown to reduce morbidity or mortality may depend on support from external sponsors, other than those sponsoring the research, as well as action by national governments.
- 9.2 Most prominent among these various issues is the extent, if at all, to which diagnostics, medicines, surgical procedures and vaccines shown to be efficacious in research will be made available in the developing country in which the research was conducted. Many have voiced the opinion that participants in research should be guaranteed access to interventions shown to be successful once the study is complete, and that to fail to do so is a form of exploitation which is ethically unacceptable (see paragraph 9.21). However, in some circumstances, the subsequent provision either of interventions shown to be successful or of a better standard of healthcare<sup>1</sup> to participants in research and especially to the wider community is not straightforward. The provision of new medicines or better healthcare is primarily the responsibility of national governments. Sponsors of research are not therefore in a position to make unilateral decisions at the start of a trial without appropriate consultation. Nor are researchers usually in a position to guarantee provision of a new intervention once they have demonstrated its efficacy and safety. However, they may and frequently do act as advocates for the provision of a medicine or vaccine shown to be successful.
- 9.3 The main purpose of conducting clinical trials is to evaluate interventions that may be applied in the wider community, of which the participants in the trial are but a sample. While this may be true in general terms, there are often significant obstacles to the application of this principle in developing countries. A new or improved treatment may be expensive. If it is, the health authorities in an economically disadvantaged country are unlikely to be able to afford its distribution to the wider population. Researchers and sponsors must understand this and justify their decision to conduct research notwithstanding, if they wish to avoid the charge of exploitation.
- 9.4 Where a form of treatment which has been developed through research proves too expensive to be provided through the local healthcare system, what, then, are the responsibilities of the researchers and their sponsors? In particular, do they have any responsibility for ensuring that it is made more widely available after its efficacy has been demonstrated in a research study? Equally, if the provision of healthcare generally for participants has been improved during the study for the purpose of carrying out the research, is there a duty to maintain this level of healthcare after the research is over and, if so, on whom should such a responsibility fall?
- 9.5 What happens once research is completed will closely reflect how the research was conducted and in what context. The health and social conditions of those participating in the research, and the standards of care provided to participants during the study are relevant to what should be

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1 i.e. better than the local standard.

provided for either these participants or the wider population at the completion of the study. When it is proposed to conduct clinical research in developing countries, the normal processes of review focus on the scientific merits and the ethical acceptability of the study. In addition, however, there is a growing consensus that the review of research should also address the issues that arise once the research is concluded.

9.6 While national and international guidance address some of these issues, the general nature of much of the guidance limits its usefulness to researchers or sponsors (Table 9.1 and Appendix 1 Table 5).

**Table 9.1**

**International guidance on provision of healthcare after the research is over and the development of national expertise**

Source	Text
<p><b>CIOMS 'International Guidelines for Ethical Review of Epidemiological Studies' (1991)</b></p>	<p>'Where findings could be applied in public health measures to improve community health, they should be communicated to the health authorities ... Research protocols should include provision for communicating such information to communities and individuals.' <b>Principle 13</b></p> <p>'While studies are in progress, particularly in developing countries, the opportunity should be taken to train local health workers in skills and techniques that can be used to improve health services. For instance, by training them in the operation of measuring devices and calculating machines, when a study team departs it leaves something of value, such as the ability to monitor disease or mortality rates.' <b>Principle 17</b></p>
<p><b>CIOMS 'International Ethical Guidelines for Biomedical Research Involving Human Subjects' (1993)</b></p>	<p>'As a general rule, the sponsoring agency should ensure that, at the completion of successful testing, any product developed will be made reasonably available to inhabitants of the underdeveloped community in which the research was carried out; exceptions to this general requirement should be justified ...' <b>Commentary on Guideline 8</b></p> <p>'An ... objective of externally sponsored collaborative research is to help develop the host country's capacity to carry out similar research projects independently, including their ethical review ... external sponsors are expected to employ and, if necessary, train local individuals to function as investigators, research assistants, or data managers or in other similar capacities. When indicated, sponsors should also provide facilities and personnel to make necessary health-care services available to the population from which research subjects are recruited. Although sponsors are not obliged to provide health-care facilities or personnel beyond that which is necessary for the conduct of the research, to do so is morally praiseworthy.' <b>Commentary on Guideline 15</b></p> <p>'Consideration should be given to whether the sponsoring agency should agree to maintain in the host country, after the research has been completed, health services and facilities established for purposes of the study.' <b>Commentary on Guideline 15</b></p> <p>'The research protocol should specify what, if any, resources, facilities, assistance and other goods or services will be made available ... after the research, to the community from which the subjects are drawn and to the host country.' <b>Commentary on Guideline 15</b></p>
<p><b>WHO 'Guidelines for Good Clinical Practice (GCP) for trials on pharmaceutical products' (1995)</b></p>	<p>'The investigator is responsible for ... ensuring that appropriate medical care and relevant follow-up procedures are maintained after the trial for a period that is dependent upon the nature of the disease and the trial and the interventions made'. <b>Paragraph 4.1</b></p>
<p><b>World Medical Association 'Declaration of Helsinki' (2000)</b></p>	<p>'At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.' <b>Paragraph 30</b></p>
<p><b>UNAIDS 'Ethical Considerations in HIV Preventive Vaccine Research' (2000)</b></p>	<p>'Any HIV preventive vaccine demonstrated to be safe and effective, as well as other knowledge and benefits resulting from HIV vaccine research, should be made available as soon as possible to all participants in the trials in which it was tested, as well as to other populations at high risk of HIV infection. Plans should be developed at the initial stages of HIV vaccine development to ensure such availability.' <b>Guidance Point 2</b></p> <p>'Strategies should be implemented to build capacity in host countries and communities so that they can practise meaningful self-determination in vaccine development, can ensure the scientific and ethical conduct of vaccine development, and can function as equal partners with sponsors and others in a collaborative process'. <b>Guidance Point 3</b></p>

For example, while the revised Helsinki Declaration (2000) refers to the need to provide those who participated in the research with access to the interventions developed during the research, and the CIOMS 1993 Guidance (Guideline 8) refers to the need to make any product developed reasonably available to the underdeveloped community in which the research is conducted, the complexity of the issues warrants further consideration.<sup>2</sup> National guidance from countries such as South Africa and Uganda also tends to be framed in general terms.<sup>3</sup> The US National Bioethics Advisory Committee (NBAC), however, in its report on clinical trials in developing countries, acknowledged implicitly the difficulties of making general recommendations to meet the needs of highly diverse situations.<sup>4</sup> In this chapter we therefore consider the issues raised and discuss how they might be resolved. They are in turn:

- the continued provision of a higher level of healthcare
- the benefits to individual participants and to the wider community arising as a consequence of the research
- the availability of an intervention shown to be successful once the research is concluded
- the long-term safety of an intervention
- the responsibilities of sponsors of research to contribute to the development of national expertise in research.

### The continuation of improvements in healthcare

- 9.7 Participants in research related to healthcare usually benefit from their participation in the research, even if they are in the control group. This may be especially the case in studies conducted in developing countries with poorly funded healthcare services, for it is often necessary to improve the local health-care system for the purposes of conducting research. For example, improved diagnostic facilities may have to be introduced to permit reliable diagnosis of the disease(s) being studied. The need for repeated clinical observations may require regular visits to a physician. Not only may this expose the participant to improved healthcare; a further consequence may be that other conditions from which a participant suffers may be diagnosed and treated even though these are unrelated to the specific research.
- 9.8 The provision of a better standard of healthcare may be particularly significant when the research is conducted with the prime objective of advancing scientific and medical knowledge without there being any immediate benefit or risk to the individuals or the community involved in the study. For example, research into the development of a vaccine may require knowledge to be gained of how individuals' immune systems respond to a naturally occurring infection. Such immunological studies are unlikely to be of immediate benefit to the participants in the research, and therefore particular value may be placed by the local participants on any improvements in healthcare that are provided as part of the study. Indeed, the provision of better healthcare may form part of the inducement to participate in research (see paragraphs 6.29–6.30).

2 World Medical Association (WMA) (2000) **Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects**, adopted by the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000. CIOMS (2001) **Draft Revision of the 1993 International Ethical Guidelines for Biomedical Research Involving Human Subjects**, CIOMS, Geneva.

3 See 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 and South African Department of Health (2000) **Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa**.

4 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**, NBAC, Bethesda, Maryland.

- 9.9 Where research studies are on a large scale, the benefits of improved healthcare provided during the research may extend to the whole community, including those not directly involved in the research. Careful attention needs to be given to how such benefits are integrated into existing healthcare. For example, it may be necessary to improve the referral systems and diagnostic facilities at outlying centres. Alternatively, routine programmes of immunisation may need to be strengthened before trials of vaccines can be conducted.
- 9.10 During the study, the researchers can contribute directly to the strengthening of local healthcare facilities. In making such a contribution, however, careful consideration needs to be given to how sustainable any changes and improvements introduced for the purposes of the research might be. This is because any improvements are usually financed out of the research funds and, thus, may not be sustained once the research is completed. Much ill-feeling may be generated, and further research in the particular community compromised, if, at the end of the study, the researchers leave and the improvements to healthcare are not sustained much beyond the end of the study.
- 9.11 To what extent healthcare improvements should be sustained after the research is completed, and by whom, are difficult issues for researchers and sponsors. The CIOMS Guidelines (1993) (Guideline 15) states that consideration be given to the maintenance of health services and facilities in the host country once the research is over (Table 9.1). Sponsors are rarely in a position to make open-ended commitments beyond the duration of the study, particularly with regard to the maintenance of facilities or the provision of medicines. However, as a minimum, at the outset of the research, thought should be given to the impact which any temporary improvement in the quality of healthcare might have and whether this can be maintained once the study is over.
- 9.12 One real contribution which researchers and sponsors may be able to make is to increase the number of people able to contribute to healthcare and to assist the development and enhancement of their skills and expertise so that there is some potential for a sustained improvement in healthcare services after the study is completed. **We endorse the 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.**

### Adverse effects

- 9.13 On occasions, a participant in a study may suffer an adverse effect as a consequence of an intervention under evaluation. Clearly, during the study the researchers have a responsibility to care for those who may suffer such adverse effects arising from the research. But, in our view this responsibility extends also to those who suffer such adverse effects after the trial is formally ended, and to those who suffer the chronic consequences of adverse effects experienced during the study. If the adverse effect is serious, it may be detected during the course of the study, in which case the research may be halted earlier than originally intended, either by the researchers themselves or after advice from the Data and Safety Monitoring Committee (DSMC). In the case of studies of a particular treatment, it may be relatively straightforward to resume treating such participants with the previous form of treatment.

### Compensation

- 9.14 The question of compensation for those injured or placed at increased risk of harm in the future as a result of research needs to be addressed. This issue was raised recently during the course of

a trial of a vaccine for malaria involving Gambian infants. Analysis of data from surveillance of participants from a pilot trial obtained after the main trial had started, suggested that vaccinated children were *more* at risk of malaria than children in the control group.<sup>5</sup> In this case, the UK Medical Research Council (MRC) provided further funds so that surveillance of participants in the trial could be intensified and facilities for the treatment of malaria in the area of the study improved. In addition, surveillance was continued for two years after the trial had been completed. Fortunately, although recipients of the vaccine were not protected from malaria by the vaccine, they were not found, on prolonged surveillance, to be at any enhanced risk of infection. No question of compensation thereby arose. Less favourable outcomes, which might raise the need for compensation, might only be revealed by routine monitoring of the participants once the trial is over.

- 9.15 It is also possible that a vaccine, a treatment or another form of intervention may be beneficial in the short term, but later have harmful side-effects. In addition, short-term side-effects may recur later. An example is the possibility that exposure to antiretroviral therapy in fetal or early life to prevent the transmission of HIV from mother to child may be associated with adverse effects in later life. This particular possibility is currently being addressed in developed countries through national and international collaborative studies, since the risk of adverse events may be small and would not necessarily be detected in a single study. If the therapy is widely used, even a small risk can pose a significant problem.
- 9.16 Researchers and their sponsors have an ethical obligation to do everything possible to minimise any harm to participants in research. If a participant in research is harmed during the course of the research, what ethical duties arise? In particular, who has responsibility for meeting any financial needs which the participant may have, for example, to pay for medical care or lost employment?<sup>6</sup> In general, responsibility for the healthcare of the participants is shared between the researchers and the local health authorities. But, if unexpected consequences do arise during the research, it is not always clear how the financial burden should be apportioned. Much of the national and international guidance addresses issues of compensation explicitly. For example, the Indian guidance stipulates that research proposals must include a mechanism for financial compensation to cover all foreseeable and unforeseeable risks (see Appendix 1 Table 3). In our view, issues about levels of compensation and who has the responsibility to provide it must be carefully considered and resolved between all those involved in the research before it begins.

### **Long-term surveillance**

- 9.17 It is unusual for a research project in a developing country to include any long-term surveillance of those participating in research after a research study has been completed. Clearly interventions may have long-term as well as short-term consequences. In some circumstances the long-term consequences may be deleterious, even though the short-term consequences are beneficial. In trials in Guinea Bissau and Senegal, high-titre (high potency) measles vaccines, when given at a younger age than normal, induced a better antibody response at that age than conventional measles vaccines. On the basis of these trials, more widespread early use of high-titre vaccines was recommended in situations in which there were high rates of infection with measles occurring earlier in childhood than the normal age at which children would be vaccinated. However,

5 Leach A, Drakeley CJ, D'Alessandro U, Fegan GW, Bennett S, Ballou WR *et al* (1995) A pilot safety and immunogenicity study of the malaria vaccine SPf66 in Gambian infants, *Parasite Immunology*, 17: 441-4; Bojang KA, Obaro SK, Leach A, D'Alessandro U, Bennett S, Metzger W *et al* (1997) Follow-up of Gambian children recruited to a pilot safety and immunogenicity study of the malaria vaccine SPf66, *Parasite Immunology*, 19: 579-81.

6 UK public sector research funding bodies such as the MRC may not, as a matter of principle established by government, offer advance indemnities nor take out commercial insurance for non-negligent harm. The MRC only offers the assurance that it will give sympathetic consideration to claims in respect of non-negligent harm arising from an MRC-funded trial.

long-term surveillance of those participating in the studies showed that girls who received the high-titre vaccines had an increased rate of mortality several years after the vaccination, from causes not obviously related to measles. This unexpected adverse effect caused the high-titre dose vaccines to be withdrawn from general use.<sup>7</sup>

- 9.18 Risk of severe infection following early preventive measures is a particular concern in the case of malaria. Ordinarily, natural and lasting immunity to malaria follows repeated exposure to the disease for those who survive such exposures. Early preventive measures, by inhibiting repeated exposure, may enhance rates of morbidity and mortality and the likelihood of severe infection in later childhood. Several large field trials have shown that bed-nets and curtains treated with insecticide reduce overall mortality in young African children by 20–30%. There is a theoretical possibility, however, that, as a consequence of this early protection, such children may be at increased risk of contracting severe malaria in later childhood. It is still unclear whether this is in fact the case.
- 9.19 The two examples cited raise the question whether investigators have an ethical obligation to undertake long-term surveillance of the populations in the study. The planned surveillance of a trial population should be so designed as to enable researchers to observe both early and late effects of the intervention being tested. Ideally, all those in a trial would be followed for an indefinite period in order to detect any long-term effects of the intervention being studied. This is rarely possible even in developed countries.<sup>8</sup> In practically all developing countries and many developed countries, such long-term surveillance has to be specifically designed and operated and is not possible within the routine system of healthcare.
- 9.20 However, a paradoxical situation may arise. If an intervention is shown to be efficacious in the short term, it may be considered unethical to continue to maintain a control group, after such efficacy has been demonstrated (see paragraph 9.27). However, when the intervention is offered to those in the control group once a trial is completed, the opportunities for longer-term observation and for the detection of later deleterious effects are lost because there is no longer a control group for comparison with the participants who received the intervention. We conclude, therefore, that the course of action adopted in any particular study will depend upon the particular circumstances: the likelihood of long-term adverse effects will have to be weighed against the likely short-term benefits. This judgement, which is not confined to clinical trials in developing countries, will have to be made on a case by case basis. It will often be difficult to make and the correct balance is often only apparent with hindsight.

### Provision of an intervention once the study is over

- 9.21 A question that researchers, sponsors and research ethics committees have to consider in research related to healthcare concerns the availability of an intervention shown to be successful to the participants in the research once the research is over. Because resources for healthcare are scarce in developing countries, this issue is often particularly difficult to address. We have seen that, for many poor people, participation in a trial may offer access to significantly better medical care and treatment (paragraphs 6.29–30). The cessation of such care and treatment, once a trial is over, has been widely criticised as exploitation of vulnerable people who generally have very limited access to healthcare and who will seldom be in a position to negotiate the extended provision of better medical care and treatment at the termination of a clinical trial.<sup>9</sup>

7 Knudsen KM, Aaby P, Whittle H, Rowe M, Samb B, Simondon F *et al* (1996) Child mortality following standard, medium or high titre measles immunization in West Africa, *International Journal of Epidemiology*, 25: 665–73.

8 The linkage of mortality and morbidity data with research studies over the long term poses substantial problems and is rarely feasible, except in specific cases, such as the link between mortality and cancer registries in the UK.

9 See, for example Glantz LH, Annas GJ, Grodin MA and Mariner WK (1998) Research in developing countries: taking 'benefit' seriously, *Hastings Center Report*, November–December: 38–42.

- 9.22 An even more difficult issue, however, is the extent of the obligation to make an intervention found to be efficacious in trials available to the wider community. Is there an ethical responsibility to ensure that an effective treatment or procedure is provided to the wider community after research is over and on whom does such a responsibility fall? In some circumstances, researchers may be in a position to take on a continuing obligation to the community in which the study was undertaken such as providing preferential access to a treatment that was developed with the co-operation of the community. It is usually difficult, however, to secure open-ended commitments to supply, for example, a new vaccine, beyond that to be used in the trial.
- 9.23 In the following sections, we consider what ought to be provided, and whose responsibility any such provision should be, to three groups of people: members of the control group in a trial, all of the participants in the research, and the wider community in which the trial took place. We first address the issue of the control group because this raises discrete questions that apply to research related to healthcare wherever it is conducted. We then go on to consider the provision of interventions to all of the participants in research and then to the wider community.

### ***Providing interventions to the members of control groups***

- 9.24 If the new intervention is shown in the trial to offer a benefit, is there an ethical obligation to offer it to the control group once the trial is complete, if they are still in a position to benefit from it? We consider that there is indeed such an obligation. In fact, such an undertaking is often given by researchers at the start of a study and may serve to persuade people to take part in the research. The nature and degree of the commitment would depend on the details of the particular study. For example, where a new medicine is being tested, treatment of the control group may be indicated when the new medicine has been demonstrated to be better than the previous one. If the new treatment is judged to be inferior, then, on the same principle, it may be appropriate to offer to treat those who received the new treatment with the standard treatment. In all cases, it should be made clear, as part of the process of obtaining consent, what is to be offered to those in the control group at the completion of the trial, and the circumstances in which it will be offered, before participants are asked to agree to take part.
- 9.25 The principle that those in the control group should be given the opportunity to benefit from an intervention found to be efficacious in a trial, is widely accepted in international guidance on controlled trials (see paragraph 5.13). Ordinarily, this is relatively straightforward for the researchers to arrange. For example, in trials of bed-nets impregnated with insecticide against malaria, those in control groups were given such nets once it had been demonstrated that the provision of nets reduced child mortality.
- 9.26 However, exceptions might arise for example if, by the end of the trial, some or all of those in the control group are not at an age, or stage of disease, to benefit from a particular treatment. In addition, it may sometimes be logistically difficult to make the intervention available to all the members of a control group. This was the case, for example, in a trial of a vaccine against infection with *Haemophilus influenzae* in The Gambia.<sup>10,11</sup> It was argued that not only would it have been difficult to locate and vaccinate those in the control group, who were entered into the trial shortly after birth, but also that, by the end of the trial, they had passed through the ages of greatest risk of infection and thus vaccination would confer very limited benefit.
- 9.27 Vaccine trials also present a further difficulty. Because most vaccines induce an immunity that declines with time, there are strong scientific grounds, when a vaccine has shown to be effective,

10 McAdam K (2002) Personal communication, MRC Laboratories, Fajara, The Gambia.

11 *Haemophilus influenzae* causes a range of diseases including pneumonia and bacterial meningitis.

for maintaining the control group so that the duration of protection induced by the vaccine can be determined. However, when the control group remains at significant risk if not vaccinated with a vaccine shown to be efficacious in the short term, such an approach would be unethical. We propose, therefore, that those in control groups should be offered vaccination with the effective new vaccine on completion of the trial, if they are still at significant risk of the disease against which the vaccine is directed. As we have said, 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.**

***Providing interventions to all the participants in a research project once the study is over***

- 9.28 Participants in research may have conditions that require ongoing treatment. In such cases, after a trial has ended, is there an obligation to continue to provide an intervention that has been shown to be effective to all the participants? Whose responsibility ought such provision to be? The revised Helsinki Declaration (2000) states that at the end of a study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified in the study. Extensive criticism has been levelled at this statement. While it is commendably aspirational in concept, guaranteeing the provision of an intervention which has been demonstrated to be successful may not be possible, especially in relation to ongoing treatment for chronic disease.
- 9.29 The NBAC Report<sup>12</sup> makes more specific recommendations about the provision for participants of treatment which has proved to be successful (Appendix 1 Table 5). It states that researchers, before the initiation of the trial, should endeavour to secure access for all participants to effective treatment after the trial and that the lack of any such arrangements should have to be justified to a research ethics committee.<sup>13</sup> The Report also recommends that research proposals should include an explanation of how any new treatment which proves to be successful will become available to some or all of the host country's population. It goes on to require that researchers must justify to the relevant research ethics committee why the research should be carried out, if this is not thought possible.<sup>14</sup> The National Guidelines for Health Research in Uganda go further. They state that the researcher must make every effort to ensure that a beneficial intervention is made available to the participants, as well as making all reasonable effort to secure its availability to the local community.<sup>15</sup>
- 9.30 The decision whether to make treatment available to participants in a clinical trial after the trial has been concluded will depend first and foremost on the outcome of the research. In practice, it may also be influenced by the cost of providing the intervention and supervising its administration. If prolonged treatment is involved, possibly for the rest of a participant's life (such as antiretroviral therapy for patients infected with HIV, or anti-hypertensive medicines for those with hypertension, which affects 50–10% of West African adults), it may be beyond the resources of the local health services.

12 National Bioethics Advisory Commission (2001) **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Volume I Report and Recommendations of the National Bioethics Advisory Commission**, Bethesda, Maryland, USA.

13 National Bioethics Advisory Commission (2001) **Ethical and Policy Issues in International Research**: Recommendation 4.1.

14 National Bioethics Advisory Commission (2001) **Ethical and Policy Issues in International Research**: Recommendation 4.2.

15 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**.

- 9.31 On examination, it might be shown that, if a pharmaceutical company were to provide the medicines required for the research, and the treatment were shown to be successful, this would be commercially advantageous, such that the costs of continuing to provide the treatment to participants in the trial could be offset. We repeat that it is very important that these issues be considered at the planning stage of any research, rather than debated or negotiated during the study or at its end. **We therefore endorse the 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.**<sup>16</sup>

### *Providing interventions to the wider community and beyond*

- 9.32 Can it be ethical to conduct research when there is little chance of making treatment shown to be successful available to the wider community? Researchers and sponsors of research have looked to international and national guidance to help them to resolve this issue. However, as we have noted, international guidance is principally in a general form and frequently difficult to apply in practice. There are, moreover, many social, political and economic factors which will influence the likely availability of a treatment shown to be successful and not all of these can be anticipated.
- 9.33 Several questions arise from consideration of the guidance on the availability of an intervention shown to be successful after the completion of the research, with respect to the range and scope of the responsibilities, and on whom such responsibilities fall:
- Should provision of an intervention shown to be successful be limited to the participants in research, or extended to others in the same community? If the latter, by whom?
  - What is the degree of efficacy that an intervention must demonstrate, in order to warrant extensive distribution and who should provide it?
  - Should all with a perceived need in the country receive the intervention and if so, for how long and who should provide it?
  - Should the intervention be provided to other (neighbouring) countries which could benefit from it and who should provide it?

These questions will become increasingly pressing as more interventions, which have the potential to benefit large numbers of people are tested in developing countries. It is clearly difficult to formulate general guidance which satisfactorily addresses the wide range of different forms of intervention.

- 9.34 A fundamental problem that must be acknowledged is that current guidance fails to reflect the reality that only rarely does a single research study lead to the discovery of a new intervention that can be introduced promptly into routine care.<sup>17</sup> For example, before mefloquine was registered as an antimalarial medicine, the WHO Special Programme for Research and Training in Tropical Disease (TDR) conducted 18 studies on three continents. Secondly, even when clinical trials have established the safety and efficacy of an intervention, there is likely to be a need for additional research studies to define the place of the new intervention in the healthcare system. Further, those participating in the trial may not be representative of the wider population, or the intervention may not be equally efficacious in another setting. For this reason, the trial may need to be repeated elsewhere and in a different setting. Research may also be necessary to determine

<sup>16</sup> National Bioethics Advisory Commission (2001) **Ethical and Policy Issues in International Research**: Recommendation 4.1.  
<sup>17</sup> This point also has a bearing on the question of whether it will be appropriate to continue to provide a successful treatment to the research participants once the research is over (see paragraphs 7.24–7.27)

the most effective and feasible means of making the intervention available and of achieving high uptake and acceptance by the local population. In addition, while clinical trials may show that, for example, a new antimalarial medicine is highly efficacious, policy-makers may decide to hold it in reserve while current treatments are still proving effective in order to delay resistance to the new treatment developing.

- 9.35 The cost effectiveness of any new intervention will also affect any decision as to its availability on a wide scale. One example of the need for cost-benefit analysis is provided by the early trials to assess the efficacy of antiretroviral treatment in reducing the transmission of perinatal HIV. The trials were performed in settings where appropriate counselling and facilities for HIV testing in pregnant women could be ensured, and where the infrastructure was such that the women were seen in hospital prior to delivery and the babies were delivered in the hospital with appropriate support and care.<sup>18</sup> However, this setting is not typical for women in many developing countries. A significant proportion live in rural communities with no access to counselling and testing facilities, and many undergo home deliveries. Nevertheless, following trials demonstrating the efficacy of the treatment, programmes to make the treatment available more widely were set up. These programmes were funded by a large number of national and international agencies, and assessed the feasibility and obstacles that needed to be overcome before the intervention could be extended into the wider community and nationally.
- 9.36 A further difficulty is that the responsibility for making a vaccine, treatment or other intervention available will not lie solely with any one group. If a national government has agreed to allow a trial to take place, it presumably accepts some responsibility to act on the results. However, some form of external aid or subsidy may be necessary before any intervention can be made more widely available and there will need to be negotiations between the various interested parties.

### ***The role of researchers***

- 9.37 There is general agreement that researchers have some responsibility regarding the provision of an effective intervention after a trial has ended, but disagreement about how far that responsibility extends. Certainly, the main function of the researchers is to undertake research. They cannot be expected to adopt a leading role in making effective interventions available. Nevertheless, most people would agree that the researcher should present findings in such a way that healthcare policy-makers can understand their implications and, at the least, the findings can be used for advocacy purposes with respect to the future provision of the intervention.
- 9.38 Fundamentally, it is policy-makers who have the prime responsibility to implement changes in healthcare and to seek evidence to inform their decisions. For example, as early as the 1950s, clinical research demonstrated that the administration of at least two doses of tetanus toxoid to pregnant women could prevent neonatal tetanus. Although most health authorities in developing countries have adopted this practice, WHO estimated that there were still 270,000 cases of neonatal tetanus in 1998.
- 9.39 While researchers are generally not in a position to translate their research findings into action when an intervention proves to be efficacious, they can draw attention to problems which have been neglected, or conditions whose impact has been underestimated, and demonstrate that there are feasible solutions. For example, a package of simple affordable measures which reduced child mortality was identified in Nigeria in the 1960s, some of which were quickly adopted by a number of developing countries. These measures later formed the basis of UNICEF's global strategy for its programme in child survival based on GOBI-FFF (growth monitoring, oral

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18 Shaffer N, Chuachoowong R, Mock PA, Bhadrakom C, Siriwasin W, Young NL *et al* (1999) Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial, *Lancet*, 353(9155) 773-80.

rehydration, breastfeeding, immunization, food supplementation, family planning, and female education). The researchers could not ensure that the Nigerian health authorities would adopt the methods demonstrated by their studies. In fact, Nigeria has been very slow in implementing the programme as originally designed or as modified by UNICEF.<sup>19</sup> Despite this, the research was very valuable in its advocacy of improved care for children. The iodination of salt to combat goitre in Nigeria (see Box 9.1) provides a further example of, on the one hand, the important role as advocates of better healthcare which researchers can play, while on the other hand, illustrating the limited influence that researchers may have in bringing about the prompt provision of effective interventions.

### BOX 9.1 Iodination of salt

In 1975 a group of scientists led by the Chairman of the Nigeria Medical Research Council presented research data to the Nigerian Department of Health which revealed the high prevalence of goitre in the country. Attention was drawn to the impact of iodine deficiency not only in causing goitre but also in reducing the intellectual capacity of children born to iodine-deficient mothers. The group urged the government to introduce iodination into the two salt factories in which the government had investments. UNICEF had offered to cover the cost of modifying the equipment to accommodate the iodination process. It took a further 15 years of lobbying before the Ministry of Health took action.<sup>1</sup>

1 Lucas A (2001) Personal communication, Harvard University.

- 9.40 A further important role of researchers is to inform local health authorities and participants about the results of their research at the end of a study. This should be accompanied by an explanation of the implications of the results for future healthcare, or prevention of disease in the community. How such information is provided will vary in different circumstances, but as well as a written report and a verbal presentation, researchers have an obligation to answer any questions that participants or other members of the community may have about the nature and significance of their findings. The appropriate forum for this is often a public meeting. It should be noted that failure on the part of researchers to present the results of a trial is a frequent reason for participants' unwillingness to participate in any subsequent research.

### ***The role of sponsors, international agencies, governments and other bodies***

- 9.41 If sponsors of research were required to fund the future provision of interventions shown to be effective to research participants or the wider community, many would cease to support such research. Sponsors from the public sector, such as the UK MRC or US NIH, would simply be unable to bear the costs involved without curtailing other research. Although the financial resources of many pharmaceutical companies are large, many of them would be equally reluctant to take on the additional burden of long-term commitment.
- 9.42 Any intervention shown to be effective in a research study may not be generally adopted because of cost. Although a successful national trial of bed-nets treated with insecticide in The Gambia reduced overall child mortality from malaria by approximately 30%, it was decided by the researchers, sponsors and the Gambian Ministry of Health that when the research was implemented nationally the cost of the insecticide would have to be recovered because the Ministry could not afford to provide free insecticide indefinitely. Charging for insecticide led to a reduction in the number of young children sleeping under an insecticide-treated net from around 70% to 20%.<sup>20</sup>

19 Lucas A (2001) Personal communication, Harvard University.

20 Cham K, Olaleye B, D'Alessandro U, Aikins M, Cham B, Main N *et al* (1997) The impact of charging for insecticide on the Gambian national impregnated bednet programme, **Health Policy and Planning**, 12: 240-7.

- 9.43 It should be borne in mind that while interventions may initially be too costly to be made available, costs may subsequently fall. This was the case with the hepatitis B vaccine used in The Gambia (see Box 1.3). On occasions, manufacturers of vaccines or sponsors of research might agree to supply substantial quantities of a vaccine free or at subsidised cost after the successful completion of a trial. This was done, for example, following trials of *Haemophilus influenzae* (Hib) vaccine in The Gambia, but it was not possible to secure an initial commitment beyond five years.<sup>21</sup> The issue of how large a population might be included in such a scheme also arises. The Gambia is a small country (about one million inhabitants), and commitments extending to much or all of the country have been secured following trials there. Such a commitment may be much more difficult to secure in a larger country, for example Nigeria or India, such that it might have to be limited to a region, or part of a region. The pharmaceutical industry is involved in various donation programmes and partnerships (see paragraph 2.35). An example is the ongoing donation of Ivermectin. This treatment, originally developed for treating animals for worm infestation, was found to be highly effective against onchocerciasis (river blindness) in humans, but was too expensive for use in developing countries. However, the pharmaceutical company that produced the medicine decided to provide it at no cost for the treatment of onchocerciasis and WHO has managed the distribution to countries in onchocerciasis-endemic areas.
- 9.44 In some circumstances, the results of a successful study may influence national policy and bring pressure to bear on providers of health services to make the intervention available. In a recent study in Uganda, oral nevirapine was administered to pregnant women infected with HIV at the onset of labour, and the newborn babies received nevirapine syrup within 48–72 hours after delivery. The study showed a 50% reduction in transmission of HIV-infection from the mother to the baby at 14–16 weeks in the group receiving nevirapine, compared to the control group which received AZT alone. The Ugandan government acted on the findings of the study and introduced a policy of providing the treatment involving nevirapine to all pregnant women who were HIV positive. The cost of treatment is relatively low, about US \$4 per person, but this is still more than most countries in which HIV is endemic can afford. The pharmaceutical company concerned has recently announced that it will offer the medicine free of charge for use in the prevention of transmission of HIV from mother to child in developing countries.<sup>22</sup> That said, the programmes of treatment do not depend merely on the cost of the medicines. It is the voluntary counselling and testing, an integral part of these programmes, as well as the need for an appropriate infrastructure for the delivery of healthcare that account for the greatest cost. Finally, quite apart from considerations of cost it is important also to bear in mind the broader benefits for women and infants that may arise from a more widespread improvement in antenatal care. These examples have led us to conclude that the fact that a particular intervention is currently expensive should not necessarily rule out the possibility of its being evaluated in a developing country.
- 9.45 As we have seen, the costs of some interventions shown to be successful may not decline significantly until some time after the conclusion of the research. To describe all such research as therefore unethical may lead to the loss of opportunities to improve healthcare. At the same time, several factors would need to be taken into account before the testing of costly medicines could be justified, including the extent of the prevalence of the condition being studied in those participating in the research, whether the disease is acute or chronic, and the complexity of and feasibility of delivering the regime of treatment. In particular a research ethics committee would need to be persuaded of the need to carry out the study in a particular community. Whether or not provision for ongoing

21 McAdam K (2002) Personal communication, MRC Laboratories, Fajara, The Gambia.

22 Boehringer Ingelheim has offered to supply VIRAMUNE® (Nevirapine) free of charge for the prevention of mother-to-child transmission in developing economies. Supplies of medicines have already been made to the Republic of Congo and to Senegal.

treatment beyond the end of the trial are in place should also be clearly explained to prospective participants before their consent is sought.

- 9.46 While the prime responsibility for continuing healthcare in a community lies with the local health authorities, we take the view that researchers also have some responsibility for what follows from the research which they conduct. A close dialogue should be maintained with the local authorities before a trial begins and at all stages of the trial. For an intervention which has a low cost, the issue of its continued availability to participants may not arise, except for concerns as to whether there is the necessary infrastructure to deliver the intervention, although in poor communities this is often a very significant consideration. For interventions which have a high cost, as we have seen, continued availability may be much more problematic.
- 9.47 Of particular concern has been the suggestion that some clinical trials in developing countries have been conducted not for the benefit of those in developing countries but largely for the benefit of those in developed countries. A possible example may be the evaluation of low cost schedules of HIV treatment (see Box 1.2). While finding less expensive, but effective, treatments for infection with HIV is a high priority for developing countries, it would also be of significant interest to developed countries. It should be recalled that the price of cheaper treatments may still be beyond the resources of most developing countries.
- 9.48 **In light of the issues discussed above, 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**
  - **the possibility of introducing and maintaining the availability to the wider community of treatment shown to be successful.<sup>23</sup>**
- 9.49 **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.<sup>24</sup>**

### The development of expertise in research

- 9.50 In 1990, the Commission on Health Research for Development identified the strengthening of expertise in research as 'one of the most powerful, cost effective and sustainable means of advancing health and development'.<sup>25</sup> During the decade which followed, efforts were made to strengthen expertise in research by national and international organisations. However, these

23 This consideration is especially important for expensive interventions.

24 National Bioethics Advisory Commission (2001) **Ethical and Policy Issues in International Research**: Recommendation 4.2.

25 Cited in Health Research for Development: the continuing challenge, a discussion paper prepared for the **International Conference on Health Research for Development**, 10-13 October 2000, Bangkok.

efforts have been criticised for being fragmentary and not sufficiently endorsed and advanced by individual countries.<sup>26</sup> Indeed, very few developing countries have a systematic plan for developing such expertise. Despite the great need for research to identify the most effective healthcare interventions for developing countries, the extent of expertise to undertake this task at a local level is severely limited. This is due largely to insufficiently trained personnel and a lack of a critical mass of researchers. The few who are well trained and able are often in great demand and may be recruited by multinational companies or international health agencies, further reducing the expertise available for areas of national priority.<sup>27</sup> It is very important, therefore, that research in developing countries, particularly when sponsored by developed countries, is used as a platform for enhancing the skills of scientists in those developing countries. The concept of 'safari research', in which the researcher from a developed country visits a developing country merely to collect samples or data to be studied elsewhere, is ethically unacceptable.

- 9.51 Genuine partnerships should be promoted in order to strengthen expertise in research and institutional development and to maximise opportunities for the transfer of skills and knowledge. Genuinely collaborative research projects generate opportunities for training and for developing human resources. Such collaborations can increase self-reliance in developing countries, thereby enabling local specialists to identify areas needing research and to develop local solutions to public health problems. The development of operational guidelines for healthcare, systems for surveillance and management flow-charts are potential by-products which in turn contribute to the improvement of healthcare systems and the ability of countries to respond to their public health needs.
- 9.52 Once research is completed, there are occasions on which complicated and expensive research equipment may be left behind, or donated by the researchers from the developed country. If local scientists and technicians have not received sufficient training to maintain and use the equipment effectively, or if resources for maintenance of equipment are not available, the opportunity for improving the ability to conduct research locally will be lost. Funds for the maintenance of equipment and development of appropriate training programmes need to be included in the costs of the original research project. Equally, the costs of facilitating training, so as to ensure that equipment can be used and is maintained beyond the particular research project, should be considered. We note that guidance such as that of the Medical Research Council of South Africa (2002)<sup>28</sup> explicitly emphasises the need for the development of research expertise to be addressed before research is conducted. **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.**

26 Neufeld V and Johnson N (eds) (2000) **Forging Links for Health Research. Perspectives from the Council on Health Research for Development**, International Development Research Centre, Ottawa, Canada.

27 Neufeld V and Johnson N (eds) (2000) **Forging Links for Health Research. Perspectives from the Council on Health Research for Development**, International Development Research Centre, Ottawa, Canada.

28 Medical Research Council of South Africa (2002) **Guidelines on Ethics for Medical Research: General Principles**, Medical Research Council of South Africa, Tygerberg: Paragraph 11.4.4i.