Chapter 1

Introduction

The scope of the Report

1.1 The purpose of this Report is to examine the ethical issues raised when research involving human participants, particularly clinical research, carried out in a developing country[1] is funded or undertaken by agencies or researchers from outside that country. This Report sets out the context in which discussions and decisions about research on healthcare in developing countries take place. It highlights the health problems that are faced on a global scale, the issues which arise when setting national priorities for research related to healthcare and the social and cultural contexts in which research is conducted. The Report sets out a framework for considering the ethical issues raised by externally-sponsored research related to healthcare in developing countries and provides an outline of the current guidelines governing the conduct of such research. It then focuses on the ethical issues which arise in four primary areas: standards of care; consent; review of the ethics of research; and what happens once research is over. In considering these issues solely in the context of research which is externally funded, we do not suggest that the ethical principles which apply to internally-funded, national research are in any way different.

1.2 The Working Party was conscious that many of the questions raised in this Report were intimately related to more general issues about economic disparities, injustice, deprivation, and exploitation. Although these broader issues are not addressed in depth, their impact on research related to healthcare and health provision is considered throughout. The Report does not set out guidelines for the conduct of research, but analyses the ethical issues involved in the current debates and recommends ways forward. We hope the Report will make a significant contribution to international debate on these topics and will be of use to those with an interest in this area, including researchers, sponsors and policymakers who will be involved directly or indirectly in research related to healthcare.

Background

1.3 Health has many determinants. These include social, cultural, economic, and environmental factors, genetic variation, and the quality of healthcare available. Research into these factors is an essential component of improving health and healthcare in developing and developed countries alike. Basic research into causes of diseases and possible treatments is also vital. The improvement of health worldwide therefore requires a continuing commitment to learn from the results of carefully designed and managed research studies involving individual participants and populations.

1.4 In the developing world, research to find new or improved medicines and vaccines is often given high priority. In many circumstances this is appropriate, but research to find better ways of delivering existing products and services to those in need is often equally or more important. Furthermore, 'non-medical' research such as that into provision of improved sanitation, clean water, better nutrition and personal preventive measures may impact on many diseases. The control of HIV infection requires not only research on treatments and potential vaccines, but also studies of behaviour. Thus a spectrum of research may benefit developing countries, ranging from research into genetic determinants of health and disease at one end to pragmatic means of implementing effective treatments at the other.

1 The Working Party debated at length the appropriate terminology to use to distinguish between countries at different levels of economic development, conscious that any classification of countries as 'developed' or 'developing' would be subject to dispute, and to change. It was decided to use the terms 'developed' and 'developing'. While these terms have limitations, they also have a certain currency and are generally understood.

1.5 Eighty percent of the world's population lives in developing countries, where both healthcare and research related to healthcare are severely constrained by limited financial and human resources, and by the lack of appropriate infrastructure to deliver healthcare. The imbalance between the need for means of prevention and treatment of disease and the ability to meet these needs is widely recognised. Research related to healthcare carried out in developing countries, often sponsored by developed countries, has made many outstanding contributions to the understanding, prevention and treatment of disease. This is not a recent phenomenon: research on diseases such as malaria, yellow fever and sleeping sickness has been carried out in what are now regarded as developing countries for more than a century.

1.6 An increasing amount of research related to healthcare is being supported in developing countries by governments, government agencies and voluntary organisations in developed countries, in addition to international bodies such as the World Health Organization (WHO) and multinational pharmaceutical companies. While some forms of sponsorship have been altruistic, others have been driven by academic interests which may not reflect national priorities for research in the country in which the research is to be conducted (see Box 2.6) or by economic considerations related to the marketing of healthcare products.

1.7 Wherever research is conducted, not only should the quality of the research be the same, but the value and respect given to participants in research should be equal. In developing countries the social, cultural and economic contexts in which research is conducted often differ from those in developed countries. Although there is broad agreement about the general ethical principles which apply to research related to healthcare, namely the duty to alleviate suffering, respect for persons, sensitivity to cultural differences and the duty not to exploit the vulnerable, there has been wide debate about the application of these principles in different research settings. Although the various international guidelines on research related to healthcare have provided some broadly based guidance, they have proved to be somewhat difficult to reconcile and apply in practice.

1.8 These difficulties were highlighted by the international controversy about a series of clinical trials into the prevention of mother-to-child transmission of HIV in 1997 (see Box 1.2). A deeper ethical analysis is therefore required not only to resolve inconsistencies in the guidance but to contribute to an improvement in practice. The most controversial aspects of research relating to healthcare in developing countries concern the process of consent to participate, the 'standard of care'[2] which is provided to participants in research and what happens once the research is over.

Consent

1.9 If research on healthcare is to be ethically acceptable, participants should be given the relevant information in a comprehensible manner, and must freely consent to take part. This is particularly important in developing countries where many participants consent to research because they believe it is their only means of receiving healthcare or other benefits. The procedures for consent that are used in developed countries may be ineffective or inappropriate in some developing countries because of differences in social and cultural environments. For example, participants in research may feel much more able to discuss research and ask questions within a meeting of the local community than on a one-to-one basis with researchers. In some regions, individuals may feel unable to refuse to participate in research that their elders, family members or community have assented to.

2 We are using the term 'standard of care' to mean the nature of the care and treatment that will be provided to participants in research.

1.10 The securing of genuine consent may also be complicated when communities in which research is to be conducted lack familiarity with the basic concept of medical research. Particular difficulties may arise when consent needs to be recorded in illiterate populations. The application of safeguards to protect such participants from possible exploitation is illustrated by the trial of vaccines for leprosy in Box 1.1. In some regions, participants may be unwilling to sign consent forms in the belief that they are signing away rights, or that other adverse repercussions may follow, such as stigmatisation following a positive HIV test (Box 1.1).

Standards of care

1.11 Much recent controversy has focused on the level of care provided to the control group in clinical trials. Should the control group receive the best current treatment available anywhere in the world, or treatment based on an alternative standard of care which takes local circumstances into account, such as the best treatment currently available in the country in which the research is being conducted? Where the best current treatment is inexpensive and simple to deliver, the answer is clear. However, in many circumstances the best current treatment available anywhere in the world may be very difficult to provide in developing countries. International attention was focused on this issue in 1997 when US-sponsored research into means of preventing mother-to-child transmission of HIV in Thailand was criticised as being unethical. The research used a locally-relevant standard of care (the control group received a placebo[3]) which would not have been acceptable if the research had been conducted in the US (see Box 1.2).

BOX 1.1 Towards an appropriate consent process: research into leprosy in Venezuela

In one study of a vaccine against leprosy carried out in rural Venezuela, researchers and prospective participants had no previous experience of an informed consent procedure. A process was designed in which the principal researcher visited communities where the research was to be conducted and explained it to community leaders. Following the approval of the community leaders, the research was explained to the community, followed by a question and answer session.

One to two months later members of the Ministry of Health visited the communities and asked individual participants if they understood what the research was about and whether or not they wished to participate. As many participants were not literate, their decision was recorded by a government worker, or in the presence of such a worker, without any of the researchers being present. Individual decisions were recorded and each participant either signed a form or gave a fingerprint.[1]

Written consent and confidentiality: HIV research in the Ivory Coast

A recent research programme which investigated possible methods of reducing mother-to-child transmission of HIV in the Ivory Coast, experienced low participation rates because of the requirement for HIV testing of pregnant women. This reluctance to be tested was due in part to the fear of social exclusion should relatives and, in particular, a husband or partner, become aware of a positive test result. The requirement for written consent to allow the HIV tests to be carried out led to considerable concern about breaches of confidentiality and subsequently, low participation rates.[2]

1 Bloom B (2001) Personal communication, Harvard School of Public Health and Convit J, Sampson C, Zuniga M, Smith PG, Plata J, Silva J *et al* (1992) Immunoprophylactic trial with combined Mycobacterium leprae/BCG vaccine against leprosy: preliminary results, **The Lancet**, 339(8791) 446–50.

2 Coulibaly D, Msellati P, Dedy S, Welffens-Ekra C and Dabis F (1998) Attitudes and behavior of pregnant women towards HIV screening in Abidjan (Ivory Coast) in 1995 and 1996, **Sahté**, 8(3) 234–8.

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

BOX 1.2 Standards of care

Research to prevent perinatal transmission of HIV in 1997

In September 1997, a paper by Lurie and Wolfe[1] and an editorial by Angell in the New England Journal of Medicine,[2] and an editorial in The Lancet[3] criticised placebo-controlled trials of short-course zidovudine given to HIV-infected pregnant women to prevent mother-to-child HIV transmission. The trials, some of which were conducted under the aegis of the Joint United Nations Programme on HIV/AIDS (UNAIDS), WHO, Centers for Disease Control and Prevention (CDC) and National Institutes of Health (NIH), were designed to determine whether relatively affordable and more feasible shorter courses of zidovudine given to pregnant women in developing countries would reduce the risk of mother-to-child transmission. They were conducted in countries where conventional local pregnancy care did not include antiretroviral treatment. The trial designs had been approved by ethics committees in the countries in which the trials were conducted.

Longer, more expensive and complex courses of zidovudine had been shown to reduce mother-to-child transmission rates in a trial conducted in the US and France.[4] Research in which the control group would be provided with a placebo would be deemed unethical in developed countries where antiretroviral treatment is available, following demonstration of the effectiveness of long-course zidovudine. The critics of the trials of a short course of treatment argued that it was unethical to give the control group a placebo when it has already been demonstrated that the longer courses reduced transmission of the virus.

Cerebro-spinal meningitis: standard of care in vaccine trials

Cerebro-spinal meningitis (CSM) occurs in epidemic form in parts of West Africa, causing thousands of deaths in epidemic years. One approach to controlling the disease is to develop an effective vaccine. Such a vaccine would need to be tested to determine whether it was effective and possible to deliver in those parts of West Africa with epidemic CSM.

In Africa, in epidemics of CSM, hundreds or thousands of people with signs of meningitis need to be diagnosed by lumbar puncture and treated by injections or antibiotics. One dose of treatment[5] may then be sufficient and the epidemic may be managed in an open area or school building. In contrast, in developed countries a case of CSM might be admitted to an intensive care facility.

Some might argue that for a trial of a CSM vaccine in a developing country, those in the trial should be provided with the best available treatment if they contract the disease, including admission to an intensive care facility where necessary. However, it would not only be very costly but also probably impractical to make such care available. If it is unethical to conduct research into a vaccine for CSM without a 'universal' standard of care being available, it is unclear where, in Africa, such research could be conducted.

1 Lurie P, Wolfe SM (1997) Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries, **New England Journal of Medicine**, 337(12): 853–6.
2 Angell M (1997) The ethics of clinical research in the third world, **New England Journal of Medicine**, 337(12): 847–9.
3 Editorial (1997) The ethics industry, **The Lancet**, 350: 897.
4 Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ *et al* (1994) Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Paediatric AIDS clinical trials group protocol 076 study group, **New England Journal of Medicine**, 331(18): 1173–80.
5 Such as oil-based chloramphenicol.

1.12 Other issues we address in the Report are the standard of care that should be provided to participants in a trial of a preventive intervention, such as a vaccine, who become infected with the disease against which the vaccine was designed to protect. We also consider the responsibility researchers have for those participants who become ill during the research with a disease which is unrelated to the disease being studied.

Review of the ethics of research

1.13 Effective review of the ethics of scientific and medical research is essential to ensure that unethical research is not permitted. Notwithstanding that the integrity of the researcher is of critical importance, the accepted method of ensuring that unethical research is prevented is through the establishment of a system in which research ethics committees undertake independent review of scientific protocols. In developed countries and a number of developing countries, such review is a prerequisite for research involving human participants. However, properly functioning research ethics committees are often absent or under-resourced in developing countries. In addition there may not be a pool of sufficiently trained and independent personnel to serve on a committee, and committees may not have the resources required to cover their administrative costs.

What happens once research is over?

1.14 Not all research projects will have results that can be translated directly into practice: research into the natural history of a disease, or the progression of an illness, may not have any immediate practical application. Trials of a medicine may reveal that it is not as effective as expected, or is unsafe, and therefore unsuitable for general use. However, research related to healthcare is usually designed to obtain results that will lead to an improvement in the prevention, diagnosis, treatment, or cure of a disease. One issue that arises when considering whether it is appropriate to conduct a specific research study within a developing country is whether the intervention being studied is likely to be affordable in that country if it is shown to be effective. This will often not be a straightforward issue: as noted in Box 1.3, expensive interventions that may appear too costly to implement in a poor country may become affordable within a short period of time while relatively affordable interventions may still be difficult to implement. Furthermore, interventions involving expensive equipment (such as magnetic resonance imaging (MRI) scanners), highly trained personnel (such as surgeons) or large numbers of trained staff (as in some counselling programmes for sexually transmitted diseases (STDs)) are unlikely to undergo such rapid and substantial reductions in cost.[4]

BOX 1.3 After research is over: hepatitis B vaccination

At the time of a large-scale trial of a hepatitis B vaccine conducted in The Gambia (performed with vaccine donated by the manufacturer), the market price of vaccine was about US $60 per course (or US $20 per dose). However, within a few years the market price for developing countries had dropped to approximately US $1–2 per course bringing it much closer to the price that many such countries could afford.

Hepatitis B vaccine has since been introduced successfully on a national basis in The Gambia and Taiwan and has been demonstrated to induce strong and long-lasting protection against the hepatitis B carrier state (the major precursor of liver cancer). These developments have provided a very strong stimulus to find cheaper ways of producing the vaccine and for the introduction of this vaccine into the childhood immunisation programmes of many developing countries.

1.15 Issues we discuss in the Report include whether it is acceptable to conduct research if the benefits of that research will not be made available to the community in

4 A recent commentary in **The Lancet** noted that social programmes such as HIV Voluntary Counselling and Testing (VCT) had been given low priority in developing countries because of their high requirements (particularly in cost-terms) on logistics and skills. However, research in the same edition of the journal found such programmes to be comparable in cost to a number of existing interventions for HIV. See Van de Perre P (2000) HIV voluntary counselling and testing in community health services, **The Lancet**, 356(9224) 86–7.

which the research was undertaken. We also consider where the responsibility for making a successful intervention generally available belongs and what role, if any, the researchers and sponsor have. In the case of participants in research who have chronic diseases such as HIV/AIDS, we address who has responsibility for providing continuing care after the research study is completed and what the standard of care should be.