

Chapter

Standards of care

3



Standards of care

Introduction

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

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

Box 3.1: Terms used to describe standards of care

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

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

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

Guidance

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

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

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

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

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

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

³ NCOB 2002, paragraph 7.30.

Workshop discussion

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

The use of placebos**Guidance**

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

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

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

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

⁶ CIOMS 2002, Commentary on Guideline 11.

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

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

Workshop discussion

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

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

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

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

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

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

Continued

⁸ EGE 2003, paragraph 2.10.

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

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

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

The obligations of sponsors

Guidance

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

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

¹⁰ EGE 2003, paragraph 2.12.

Workshop discussion

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

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

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

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

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

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

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

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

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

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

¹¹ NCOB 2002, paragraph 7.35.

Workshop discussion

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

The provision of care for conditions related to the trial

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

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

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

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

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

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

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

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

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

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

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

The provision of care for other conditions

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

Summary of discussion on standards of care

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