temptation to oversimplify the complexity of health funding decisions. At the completion of her presentation, expert commentary was offered by Professors John Campbell, David Skegg and Murray Tilyard of the University of Otago.

The Saturday pre-lunch session offered a number of workshops and research papers. The research papers presented in this session are included in this special issue of the *Report*.

The afternoon sessions discussed issues relating to integrated care and good practice guidelines. The afternoon began with a plenary discussion by Catherine Te Miringa Holland (Tainui and Ngai Tahu, Business Health and Management Consultant), Mark Jeffery (Medical Oncologist) and Professor Murray Tilyard (Professor of General Practice). Catherine Holland's talk outlined how integrated care meant that health care for Tainui Maori could be delivered in a manner which was much more effective and appropriate than the previous more centrally controlled method of delivery. Mark Jeffery has been involved with the National Health Committee in the development of good practice guidelines. He observed that these involve the systematic review of clinical literature to determine optimal practice and, further, that they ought to be distinguished carefully from clinical protocols.

Professor Tilyard leads a very large group of general practitioners operating with budget holding practices. He argued that integrated care meant that health care funding could be targeted more effectively.

Following the plenary sessions, seminar participants moved into workshop groups to discuss the material presented in the plenary session. These groups reassembled at 4.15 pm and presented questions to the panel.

On Sunday the direction of the Seminar changed to a consideration of the 'Edges of Life'. Seven workshops were held covering the topics of Resource Allocation in the withholding and withdrawal of treatment, the posthumous use of gametes, the use of foetuses for treatment and research, management of the dying process, the foetus as patient, resource allocation (withholding and withdrawing treatment).

The 11am session was a hypothetical discussion led by Grant Gillett. The hypothetical format proved to be a good way to summarise issues discussed at the seminar.

The organising committee for the workshop (Donald Evans, Barbara Nicholas, Grant Gillett, Andrew Moore, Nicola Peart) are to be commended for bringing together such a collection of experts on important and current New Zealand issues in Bioethics.

Fay McDonald was the organiser for the Summer Seminar, without her capacity for handling the complexities of conferences, the Summer Seminar could not have run as efficiently as it did.

Article

Research Ethics in Poor (and not so Poor) Countries

Andrew Moore

Department of Philosophy, University of Otago

This paper was presented at the 1998 Bioethics Summer Seminar

How commonly in a country such as New Zealand do health professionals now find themselves unable to offer services to the standard of the best known treatment or care in the world? Hold onto your answer. I return to this question below.

Turn now to a very different set of issues. As is well known, there are catastrophic problems of HIV and AIDS worldwide, but especially in Africa. Reputable current predictions are that 6 million pregnant women on that continent will have HIV infection by the year 2000 (Scarlatti; Lurie and Wolfe, 853). One part of this problem concerns transmission of the virus during pregnancy from mother to child. It is by no means the only part of the problem, nor even perhaps the most important, but it is a key focus of this paper. Right at the end, I turn very briefly to wider issues.

Research findings in the mid 1990s demonstrated decreases in transmission rates from pregnant HIV-positive women to their children of 50 per cent or more, with a course of zidovudine (hereafter, AZT) (Lurie and Wolfe, 853). But the treatment is complex, and far too expensive for poor countries to be able to introduce it as their new standard of care. Urgent research is consequently underway in search of something effective, but much cheaper.

At least two sorts of clinical trials seem relevant. AZT-equivalence trials look at whether there might be something just as effective as, but much cheaper than, the AZT regime now standard in rich countries. The earlier research suggested in particular that courses of AZT shorter than those so far of proven value might be equally effective (Lurie and Wolfe, 854). Placebo-superiority trials look at whether there might be something affordable by poor countries that is more effective than their currently available treatment. Here treatments such as intrapartum vaginal washing, vitamin A derivatives, HIV immune globulin, and very short-course AZT are compared to placebo, on the pessimistic assumption that placebo is approximately as effective as no treatment at all. Studies of both sorts have in fact been approved, and are currently underway (Lurie and Wolfe, 853; Angell, 848).

Are the AZT-equivalence trials ethically acceptable? Are the placebo-superiority trials ethically acceptable? Several writers in the *New England Journal of Medicine* (hereafter, NEJM) have vigorously responded 'yes' and 'no', respectively (Angell; Lurie and Wolfe), and the controversy has

spread to *The Lancet* and *The Economist*. This paper critically examines the issues of clinical research ethics at stake in the debate.

The recent NEJM writers appeal to the following well-established orthodoxies of research ethics to make their case against placebo-superiority trials:

(1) Equipoise: any clinical trial in a therapeutic setting is ethically acceptable only if there is justifiable uncertainty over whether any treatments under study in that trial are better than any others. (Freedman; Angell, 847; Lurie and Wolfe, 854)

(2) Best treatment: any clinical trial in a therapeutic setting is ethically acceptable only if, at least in-trial, all trial participants receive the best known existing treatment. (Declaration of Helsinki; Angell, 847; Lurie and Wolfe, 853)

AZT-equivalence trials pass these two tests. Placebo-superiority trials can be designed which pass the equipoise test, but since we know that long-course AZT is better than placebo, they cannot pass the best treatment test. Given these orthodoxies in research ethics, the NEJM writers give the right answers to the questions posed above. But perhaps the orthodoxies themselves should not just be taken as given.

Let us first review the ethics of AZT-equivalence trials. Since long-course AZT is considerably better than placebo, some children will survive HIV-free in a trial of this sort in Africa who would have died, had it not been conducted. If such a trial finds a cheaper and equally good alternative to long-course AZT, then some people in rich countries like New Zealand and the United States will also benefit through consequent cost-savings on our current standard treatment for women without previous exposure to AZT. It is very unclear, however, whether such findings will benefit anyone in a poor country who is not a trial participant. Long-course AZT is very expensive indeed, and an equally effective alternative would have to be far cheaper if it were to be affordable in poor countries. If shorter course AZT is found to be approximately as effective, some might think this will combine with the benign effects of AZT price reductions over time to trickle benefits down to these people. But this speculation can hardly be relied on to deliver the medicine. It is strongly counteracted, in any case, by the fact that in this area, as in many others, the best existing standard of care is constantly advancing, in both effectiveness and cost. Orthodoxy's best treatment claim might allow an AZT-equivalence study today, but is likely next year to allow only an AZT+-equivalence trial. A couple of years after that, it is likely to allow only an AZT++-equivalence trial. And so on. An AZT-equivalence trial might be of vital benefit to some of its poor participants, so it should not be ethically written off. But even if its findings are more widely valuable, it is far from clear that any of these wider benefits will be felt by poor people outside the trial itself.

Now revisit the ethics of placebo-superiority trials, taking the issues in parallel to those discussed above for AZT-equivalence studies. Since very short-course AZT, vitamin A derivatives, intra-partum vaginal washing, HIV immune globulin, and even placebo might be considerably better than no treatment at all, some children might survive HIV-free in a trial of this sort in Africa who would have died, had it not been conducted. If one or more affordable alternatives is better than placebo, then children of HIV-positive women in rich countries like New Zealand and the United States might also benefit, but probably not, since the cheap new find is unlikely to be as effective as our current standard treatment. Given that placebo-superiority should only be tested against alternatives confirmed to be affordable, on the other hand, we can be sure that if one or more of the alternatives is effective, wider benefits really will be felt by many poor people beyond the trial. In advance of actually conducting the research, it is hard to say for sure whether an AZT-equivalence trial or a placebo-superiority trial is more likely to benefit the children of poor countries. There is nevertheless a wide range of possible outcomes under which a placebo-equivalence study would generate substantial benefits to these people, and an AZT-equivalence study would generate none. The reverse would occur only if researchers were to find a course of highly effective AZT short enough to be genuinely affordable for everyone who needed it in every poor country. To say the least, this is a long shot.

My interim conclusion is that, contrary to the recent NEJM writers and the clear weight of orthodoxy in clinical research ethics, both AZT-equivalence and placebo-superiority trials in poor countries are ethically defensible. If that is so, the orthodoxy itself must be mistaken. I shall now try to confirm this, by outlining its further unpalatable implications for both poor and not so poor countries.

Some argue that if there is more than one otherwise ethically acceptable study design in a given area of research, we are ethically obliged to choose the one that will minimise loss of life (Lurie and Wolfe, 854). This claim seems plausible, and I did also agree above that more child deaths will occur within placebo-superiority trials in poor countries than within AZT-equivalence trials, I too might thus seem committed to ruling out all placebo-superiority trials. But matters are not so simple.

To keep the fundamental issues clear, assume that an AZT-equivalence trial, rather than a placebo-superiority trial, is conducted in a poor country. Because we know already that AZT is better than placebo, one result of this choice would be fewer child deaths in-trial. A wider result, however, might well be more child deaths overall in the country concerned. This would happen whenever placebo-superiority trials would deliver substantial benefits to the non-trial children of poor countries, via an affordable treatment that is better than currently available treatment, and AZT-equivalence trials would deliver no such thing. Those committed to AZT-equivalence trials might respond that researcher ethical responsibility for child deaths within their trial is much greater than it is for child deaths that might very well occur outside the trial, even if the latter group of deaths is far bigger, and is a clearly foreseeable consequence of the researchers' choice of study design. Whatever ethical cleanliness one might think this move would secure for researchers, it is hard to see why their modest gain in ethical hygiene should weigh heavily with those who fund their research. Funders might legitimately give much greater weight to progress on the overall HIV/AIDS crisis, even at some cost to the very tiny portion of it to which some commentators might hope to restrict the ethical responsibilities of researchers.

Those who argue for the rejection of placebo-superiority trials in favour of

AZT-equivalence trials are committed to a striking ethical asymmetry between in-trial and extra-trial child deaths. There are further circumstances under which they are also committed to a striking ethical asymmetry between deaths in their current trial and deaths in their next trial. As has been argued above, there is a strong possibility that an AZT-equivalence trial will not benefit any children of the poor beyond its own participants. Researchers committed to orthodoxy in clinical research ethics might then run a further study, with a different AZT-equivalence design (or AZT+-equivalence design). They might even have to try a third time. More child deaths would occur in-trial with each additional trial, and this might well add up to more child deaths overall than would have occurred, had a single placebo-superiority trial been opted for instead, and proved successful. Tenacious defenders of the AZT-equivalence research path could insist at this point that not only is their ethical responsibility for in-trial child deaths much greater than it is for extra-trial child deaths, but their responsibilities are also much greater for deaths in their current trial than for deaths in their next trial, or in the one after that. On the face of it, however, these are not ethically appealing asymmetries for researchers to defend, nor for their sponsors to accommodate. They are nevertheless asymmetries of a sort to which many popular general approaches to ethics are deeply committed (Broome, 6-10).

Return now to the question that opened this paper. It is plausible that many health professionals in New Zealand, Japan, Germany, Canada, the United States, the United Kingdom, and the like, are now unable to offer services to the standard of the best known treatment or care available in the world. It is also plausible that such treatment is also not available in many current clinical trials in these same therapeutic settings. Orthodoxy's best treatment claim strikingly implies that all these studies are unethical. In the light of this, very many research ethics committees and IRBs committed to the orthodoxy might wish urgently to review their recent approvals. Furthermore, the orthodoxy in research ethics implies that any trial within which the best known existing treatment cannot be made available also cannot be made ethically acceptable. Insofar as the best known existing treatment is reliably available only to those in certain world-leading centres, and within certain gold-plated health insurance arrangements, the orthodoxy approves therapeutic research only in those same settings. These potential research participants are the world's best-off people, among those in their particular health or illness state. Any successful research conducted with them will certainly benefit others in their well-off situations, but since the standard of care they already receive is better than that enjoyed by the rest of us, such research cannot be relied on to benefit anyone else. Orthodox research ethics implies, then, that the only ethically acceptable research in therapeutic settings takes place among the best-off.

One response to the problems canvassed above is that the orthodoxy in clinical research ethics must be right as it stands. If the arguments set out above are persuasive, however, this forces one to bite some very hard bullets. Expressions of the orthodoxy, such as the Declaration of Helsinki, are valuable but also reviewable starting points for research ethics; they should not be objects of uncritical reverence. In the present case, they simply have misguided implications. One alternative response is that even if it delivers unethical results in the cases discussed above, and in many others like them, we should still stick with the Declaration of Helsinki's unmodified claim that 'In any medical study, every patient – including those of a control group if any – should be assured of the best proved diagnostic and therapeutic method.' (Helsinki Declaration, 62-3) If we do not do so, it might be argued, researchers will start taking all sorts of unethical liberties with this, and with many other, Helsinki provisions. I have argued above that the price of this stance for research in both poor and not so poor countries is very high. We should opt for it only as a last resort. A recent editorial in *The Lancet* proposes instead that we qualify Helsinki's best treatment claim with a phrase such as 'compatible with the realities of health care in the country where the study is conducted'. This revision is rather vague, but it would allow IRBs and research ethics committees some relief from the orthodoxy. A more radical revision would instead have us add the phrase '... that would be otherwise available to trial participants, were the study not conducted at all'. Contrary to critics of the placebo-superiority HIV/AIDS trials (Angell, 849, Lurie and Wolfe, 855), this does preserve a universal standard for research ethics. It is also true that it is a universal standard that would be met in some countries by study designs that would fail it in other countries. That would happen because the new standard would universally allow researchers to take the actual local standard of care as the therapeutic baseline for the research studies. As long as the alternatives under comparison with that status quo are confirmed in advance to be affordable if effective, and as long as any low levels of actual care in a country are due neither to injustices within its health care system, nor to the researchers or their sponsors themselves, this seems to be an improvement on, and perhaps even an ultimately defensible revision of, the Declaration of Helsinki's approach to research ethics.

Return finally to the big picture of HIV/AIDS disasters in Africa. All those who have so far joined the current controversy over research ethics in these settings have assumed that it is straightforwardly a good thing to reduce child deaths caused by perinatal HIV transmission. The trouble is that these poor countries also face massive AIDS orphan problems. None of the treatments currently under trial will significantly improve the health of pregnant HIV-positive women, or the health of the equally badly off men in these countries. The brutal truth, then, is that the more children they save, the worse these treatments will tend to make the AIDS orphan problems. This illustrates again how much we miss if we confine debate about the ethics of clinical research to narrow in-trial considerations. The problems of AIDS orphans are already very serious indeed. In the short-term at least, our best response might be massively to increase international child adoptions out of the worst-affected countries. This would require us to set aside the fashionable idea that it is more important for a child to live out its life in the country – or, very optimistically, the culture – of its parents, than it is for that child to have any serious prospect of survival into a flourishing adulthood. But in family ethics, as in clinical research ethics, orthodoxy very often does not deserve its respectable reputation.

Note

I am indebted to two anonymous Otago Bioethics Report referees, and to John McMillan, Tim Mulgan, Charlotte Paul, and participants in the February 1998 Bioethics Summer School in Dunedin for very helpful discussion of issues addressed in this paper.

Bibliography

'Aids in Africa', *The Economist*, 27 September 1997.

Angell, Marcia 'The ethics of clinical research in the third world', *New England Journal of Medicine*, 337, 18 September 1997: 847-9.

Broome, John *Weighing Goods*, Oxford: Blackwell, 1991.

Declaration of Helsinki, 'Medical Research combined with professional care', 1983.

Editorial: 'Pragmatism is codes of research ethics', *The Lancet*, 351, 24 January 1998.

Freedman, B. 'Equipoise and the ethics of clinical research', *New England Journal of Medicine*, 1987, 335: 141-5.

Lurie, Peter and Wolfe, Sidney 'Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries', *New England Journal of Medicine*, 337, 18 September 1997: 853-6.

Scarlatti, G. 'Paediatric HIV infection', *The Lancet*, 348: 863-8, 1996.

At the Centre

The most significant change over the last few months has been the developments resulting from having a new director. Donald's arrival was timely, as a number of new educational initiatives are starting this year. As mentioned in previous issues of the Report, the new Patient Doctor and Society module began in 1997. It is a two-year programme for second and third-year medical students incorporating contributions from Preventive and Social Medicine, Behavioural Science and Bioethics. 1998 sees the beginning of the third-year component of the new module and the continuation of the second-year components developed last year. Planning for the new clinical curriculum (Years four, five and six of the medical programme) is underway.

Donald Evans and his successor at Swansea, Dr Martyn Evans, have written a book entitled *A Decent Proposal*. A limited number of books offer the detail necessary to be a useful guide to research ethics. The detail and accessibility of *A Decent Proposal* means that it is an ideal resource for students studying research ethics, for research ethics committee members, as well as for researchers. It is published by John Wiley Publishers. It is not yet available in New Zealand book stores and will probably be quite expensive to purchase here. For readers interested in having a copy of this publication, the best way to obtain it would be through one of the Internet book stores. We are planning to publish a review of this book in the next issue of the Otago Bioethics Report.

Jenny Conder and Maggie Oakley have had official confirmation of their Master of Health Science degrees. Jenny's thesis was about moral decision-making and paediatric decision-making, while Maggie wrote her thesis on women's experience of ultrasound screening. Everybody at the Centre congratulates Jenny and Maggie on their success and wishes them the best for the future. Bachelor of Medical Sciences student Neil Price has finished his thesis and returned to the fourth year of his medical programme. Neil's thesis concerned quality and the doctor-patient relationship. We are looking forward to seeing Neil again in the ethics sessions of the clinical course.

Reader's Views

Dear Editor

I have just read Murray Davidson's account of the 'Gene Technology: Benefits and Risks' conference that was held in Wellington on 21 August and I would like to correct an impression that he gives of points that I 'made strongly' in my own paper. I have no quarrel with the first of them – that I saw exciting progress in the near future when researchers will able to insert genes with precision into an exact location in the genome – but I would like to clarify his report that I expressed 'caution concerning the sort of legislation which banned animal experimentation', which I am reported as saying would 'destroy NZ science'.

This second comment was not in my paper, but arose during discussion (I think of someone else's paper). In that discussion, I drew attention to the legislation that was being planned with the main intention of prohibiting the cloning of human embryos in NZ. I had been reliably informed that the draft bill included a ban on all 'human-animal hybrids' – including hybrid cell lines. I pointed out that, if this really was going to be in the legislation, this would prevent NZ geneticists from making the hamster/human and mouse/human hybrid cell lines that are standard tools for human gene mapping. Even worse, it would prevent NZ scientists from making 'hybridomas' – the source of the monoclonal antibodies that are so important in just about every aspect of modern biochemical and molecular biological research.

Perhaps I exaggerated in saying that such a ban would 'destroy' NZ science, but it would certainly have a disastrous effect.

Yours sincerely,

George Petersen
Professor Biochemistry