
Editorial

Ethics, philosophy and clinical trials

Several of the many medico moral problems associated with medical experimentation are examined in depth in this issue of the Journal. Among the most challenging are informed consent, the use of animals, and the role of ethics committees. Most shocking of all however may well be the fundamental attack, by Drs Burkhardt and Kienle, on one of medical science's most respected institutions, the controlled clinical trial.

It is worth immediately distinguishing two different sorts of objection to clinical trials. The first concerns clinical trials carried out against the rules accepted by the medical community as a whole, whether these rules are technical or ethical – objections to what one might call rogue trials. The second type of objection however questions the accepted rules or principles themselves. Drs Burkhardt and Kienle have in their writings over many years waxed eloquent about rogue clinical trials, continuing a tradition started in this country by Dr Maurice Pappworth in his *Human Guinea Pigs* (1). The tradition is an important one to support, for without such vigilance even agreed standards tend to slip. The establishment of hospital ethics committees was in part a response to the important criticisms made by Dr Pappworth. More fundamental however are Burkhardt and Kienle's criticisms that clinical trials are in principle mistaken. There is a danger that the important points to be found within their discussions will be dismissed too readily, especially in the light of the vigorous criticism they have received from a variety of experts including the lucid responses provided by Professor Vere (2). Apart from Burkhardt and Kienle's claims that it is in practice extremely difficult to avoid serious technical shortcomings in setting up a statistically satisfactory trial, and that researchers often do not carry out trials according to the accepted rules, they also make two very radical claims. The first is that because random selection of trial subjects can generally not be achieved (because any group of patients comprises a highly selected *non-random* group) therefore any results validly obtained concerning the trial group cannot be generalised to apply to particular patients outside the trial group. Such generalisation they argue amounts to induction and is therefore, if one accepts Popperian epistemology as most scientists currently do, not scientifically tenable. Vere flatly denies this claim and also indicates the considerable

philosophical debate concerning the whole problem of induction. He also points out that 'if induction in clinical trials is wicked what about induction based on the experience of isolated individual patients?' However, the force of Burkhardt and Kienle's argument here, if it is right, is that extrapolation from the results of clinical trials, no matter how beautifully designed or executed these are, to individual patients outside the trial group is no more respectable *scientifically speaking* than such admittedly primitive and currently non-respectable forms of induction as extrapolation from anecdotal experiences. The claim is difficult to comprehend, so staggeringly counter-intuitive is it, given our acceptance of the clinical trial as the paradigm source of information on which to base our therapeutic decisions. But scientific paradigms have been rejected in the past (remember phlogiston) and Burkhardt and Kienle's case is that this one too should be rejected.

Suppose, however, we ignore these radical and contentious philosophical objections to the very principle of accepting that the results of properly conducted randomised controlled trials should be the basis for therapeutic decision-making, do there remain any fundamental problems? The nub of the second radical objection underlying Burkhardt and Kienle's discussion of ethical and legal problems is that the standards of probability required for scientific (statistical) validity of experimental results may be more exacting than the standards of probability implicitly or explicitly acceptable to individuals, whether they be doctors or their patients, as a basis for taking deliberated individual action. The normal range of acceptable significance levels in biological science is from 0.1 at the 'softer' end of the science, through 0.05 for the bulk of biological investigation to 0.01 at the relatively rare precise end of the spectrum of such work. Roughly speaking this means that biological scientists agree to accept a scientific hypothesis if the experimental evidence makes the probability of it being wrong somewhere between one in ten to one in a hundred depending on the chosen significance level. Individual people however vary as to the degree of probability they are prepared to accept as justifying their actions – they vary to the extent that they are prepared to gamble or take risks. Moreover these gambles depend on their circumstances. A patient

dying from some disease for which the existing best therapy is fairly useless is unlikely to demand as high a probability that a new drug is effective as the medical scientist will demand. A ten to one, let alone a hundred to one probability that the new drug is better than the standard may well be an irrelevant luxury in the eyes of the dying patient who may settle for a one in ten, a one in a hundred or even a one in a thousand chance that the new drug will save him.

It is in this and similar contexts that 'the problem of trends' discussed by Burkhardt and Kienle (and of course by many others who are concerned) becomes important. In the process of a clinical trial being conducted under modern conditions with sophisticated sequential analysis of the results a trend will often become clear as to which of the drugs (or therapeutic regimes) is more effective. The null hypothesis that there is no difference may gradually become less and less probable as the trial progresses. Of course there's many a slip 'twixt cup and lip and it may be that the trend is bucked; that is entailed in the meaning of the term 'trend'. Nonetheless it is not *irrational* to decide to act on the basis of the trend but before the pre-determined level of statistical significance is reached. Discussing this point Professor Vere asks 'how can it ever be right to accept standards of proof, set out on the costly road to attain them and then draw back while still upon that road, having made it *seem* that justice has been done?' The answer is presumably that *qua* scientist the doctor may accept a more rigorous standard for acceptability of a theory than he would accept *qua* physician. Faced with a trend that as a doctor or a father or a husband or a patient he would act on he may nonetheless feel constrained not to act because he has previously accepted more rigorous standards of evidence as a scientist. It would surely be mistaken to believe that no moral dilemma exists in such cases. Furthermore, regardless of what the *doctor* thinks about the matter whether as doctor or scientist, the patient may very well have his own very different standards of acceptability. Why should scientists' standards prevail over his own?

Two quite different sorts of justification might be offered. The first states that from a scientific point of view lesser standards of rigour than those predetermined by the scientists are simply invalid. Thus the trends are of no significance scientifically until the predetermined significance levels are attained. Many would accept such explanations for the purposes of organising scientific endeavours but what obligations do ordinary doctors, let alone their patients, have to participate in scientific endeavour? The second line of justification might be that only by accepting scientific standards of rigour will medicine advance – or advance most rapidly – so as to benefit the sick and the dying of the future. The individual, it might be said, must bear some of the sacrifice involved in the interests of the

community at large, and especially of the sick community. Thorough-going utilitarians will find little difficulty accepting this answer, for the maximisation of welfare is the heart of utilitarianism. But those who also believe in the Hippocratic acknowledgment of the primacy of the individual patient, maintained to this day in the modern declarations of medical ethics including the Helsinki Declaration (3) which specifies that 'concern for the interests of the subject must always prevail over the interest of science and society' may well balk at imposing scientific standards of acceptability over the ordinary therapeutic standards of the doctor himself. And those who believe that respect for the individual's autonomy is a fundamental ethical principle – who believe with Kant that a person must never be treated merely as a means to an end no matter how admirable that end – they too will find pause.

Even if one accepts that to incorporate a patient in a clinical trial, even a therapeutic clinical trial, may to some extent be suboptimal so far as his or her individual medical care is concerned, in order that the rigour of scientific investigation may be attained, this need not sound the death knell of clinical trials. Rather it would require that patients were informed about these problems and allowed to make up their own minds about whether or not to participate. Nor does it seem to follow that patients must be given information on trends – it would seem justifiable to explain to them that for scientific purposes and for the potential benefit of future generations of patients the scientific rather than the personal standards of rigour must be employed, and that therefore trends will not be reported or acted upon until the required standards of significance are reached. The patient would then be free to join the trial under these stipulated conditions or alternatively to have the currently best available treatment, or even in some cases, perhaps, to opt for the trial regime *outside* the controlled randomised trial but nonetheless on a rigorously observed basis.

What does seem clear is that the scientific standards of rigour required in clinical trials may involve doctors in taking actions which, if they had only their individual patients' interests at heart, they might not wish to take. If this is so it is surely important to recognise it to be so and to make sure patients recognise it to be so.

References

- (1) Pappworth M H. *Human guinea pigs*. Harmondsworth: Pelican, 1969.
- (2) As well as his responses in this issue of the Journal see Vere D W. Controlled clinical trials – the current ethical debate. *Proceedings of the Royal Society of Medicine* 1981; 74: 85–87.
- (3) Quoted, under 'declarations', in Duncan A S, Dunstan G R, Welbourn R B, eds. *Dictionary of medical ethics*. London: Darton Longman and Todd, 1981.