Patients' preferences and randomised trials

SIR—It is perhaps a little misleading of Silverman and Altman (Jan 20, p 171)[1] to say that in the first two decades of randomised controlled trials, participating doctors were expected to enrol all their eligible patients. Ralston Paterson,[2] who nearly 50 years ago pioneered large breast cancer trials comparing the outcome after different treatment policies, always insisted that "not only must two clearly defined policies be equally acceptable" but also that "every patient must be individually reviewed before registration into the trial", the doctor concerned asking himself "am I entirely happy that, for this woman, either of the two treatments which she may get is equally applicable?". Other leading pioneers seem to have felt equally strongly about this issue.[3]

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1 Silverman WA, Altman DG. Patients' preferences and randomised trials. *Lancet* 1996; 347: 171–74.
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SIR—Schulz,[1] when considering subversion of the randomisation process by the profession, said: "Randomised controlled trials (RCT) are anathema to the human spirit; we must acknowledge the human elements of this important scientific process". He was discussing evidence that inadequate methodological approaches in controlled trials, in particular the subversion of randomisation by trialists by exploiting inadequate treatment allocation concealment (so that they might express their treatment preferences), yielded larger treatment effects than those with adequately concealed allocation.[2] Resultant bias due to inadequate treatment assignment methods was identified nearly 20 years ago, as commented upon in *The Lancet*.[3]

Silverman and Altman[4] identify the sudden fall in recruitment occasioned by the introduction of informed consent with a consequent need to explain randomisation. The early trialists' freedom for two decades from this constraint when "participating doctors were expected to enrol all their eligible patients in a given trial" portrays an ease and unanimity of action.[5] Was there better understanding at that time by the profession of the randomisation procedure than there apparently is now? Or perhaps this elite in the 1950s and 1960s would have been less inclined to subvert randomisation in controlled trials than Schulz's more recent subjects of surveys? Perhaps Schulz's belief that RCTs are "anathema to the human spirit" causes physicians to override their intellectual grasp to express profession preferences, thus introducing the very biases that the trial method seeks to avoid. The ethical implications of this practice are considerable in trials designed and offered by the profession.

Realistic assessment of all methodological shortcomings is essential, with involvement of lay people in the debate to find better ways to do quality research while heeding everyone's preferences. This change would demand better education not only of the public but also of the profession, about the basic concepts of the research process and the need for its rigorous implementation.

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1 Schulz KF. Subverting randomization in controlled trials. *JAMA* 1995; 274: 1456–58.
2 Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995; 273: 408–12.
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SIR—Silverman and Altman[1] acknowledge that patients' preferences can bias recruitment into trials, undermine the effectiveness of randomisation, and affect trial outcomes. Oddly, despite such welcome recognition, they conclude that "the RCT is the only reliable way to compare therapies" and suggest that alternatives to randomisation are needed only when "randomisation is either impossible or unacceptable to most patients".

When patients are willing to accept randomisation as their only chance of obtaining a preferred treatment, the RCT will have a biased study sample with poor generalisability. RCT participants are more likely to drop out if allocated non-preferred treatments,[2] thereby undermining randomisation. A partly randomised preference trial (PRPT) is the design of choice when some patients have strong preferences.[3] By allocating such patients to their preferred treatment before allocating those prepared to be randomised in a PRPT, most eligible patients will be recruited. The randomised patients in PRPTs are less likely to be disappointed than RCT patients and less likely to drop out. In PRPTs, randomisation can work very effectively. We can also determine how much better (or worse) treatment outcomes are when patients are given their preferred treatments.

Patients' preferences will be influenced by information available to them, including information from doctors which may be appropriately detailed, accurate, and balanced but may be less helpful, or even misleading, especially with new treatments about which little is known. A patient eligible for a trial is usually better placed than their doctor to judge which treatment would least conflict with his or her lifestyle, priorities, likes and dislikes, and personality. Silverman and Altman's distinction between "informed choice (in which patients rely on the estimates of the size of risks and benefits of proposed interventions, as reported in reliable overviews) and subjective preference (in which patients ignore the available evidence and prefer to rely on prayer, a hunch, or the advice of friends, relatives, or seers for a decision)" is a false dichotomy that risks perpetuating patronising attitudes in which patients are seen as incapable of making rational decisions. Cochrane systematic reviews of clinical trials have the potential to provide a valuable source of information both for doctors and patients. However, these current reviews give undue weight to RCTs. The focus on group effects with little attention to patients' individual differences limits the value of Cochrane reviews to patients and doctors trying to choose between treatments.

Patients who are allocated preferred treatments have reported greater treatment acceptability than have those who accepted random treatment allocation.[4] There have also been reports of patients ill-suited to the demands of a treatment being misguidedly attracted to a treatment with disastrous consequences for morbidity and mortality.[5] Only by fully reporting recruitment procedures and by further systematic study of the existence, origins, and effects of patients' preferences within clinical trials will we understand how we can help patients choose their treatments to achieve optimum medical as well as psychological outcomes for the individual concerned.

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1 Silverman WA, Altman DG. Patients' preferences and randomised trials. *Lancet* 1996; **347**: 171–74.
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SIR—Silverman and Altman[1] give only one side of one complicated argument. It is well established that in some double-blind trials people who adhere to placebo treatments are found to do better, even after assiduous adjustment for baseline risk, than those who do not.[2] Hence the belief that patients given treatments that they prefer might do better than others who are unhappy about their treatment is sometimes strongly supported. However, they go on to argue that comparison of non-randomised groups will necessarily cripple reliable causal inferences.

Randomised comparison might reduce choice for many participating patients and hence attenuate the measurement of the true maximum biological effect. Unless we know more about the importance of this matter, both in which circumstances and by how much, such discussions will inevitably be circular. Silverman and Altman suggest that to investigate the magnitude of the effects of choice, necessarily outside a simple randomised setting, is to "overlook an antecedent need to protect patients from exploitation by overblown claims of efficacy". It is precisely not to overlook such a need to protect patients from inaccurate claims that I too[3] have argued for thorough investigation of the therapeutic role of patient preferences. How otherwise could we ever know that randomised comparisons do not sometimes systematically, and possibly importantly, underestimate (or overestimate) the true potential effectiveness of some treatments?

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2 Coronary Drug Project Research Group. Influence of adherence to treatment and response of cholesterol on mortality in the coronary drug project. *N Engl J Med* 1980; **30**: 1038–41.
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SIR—Implicitly Silverman and Altman[1] accept absolute polarisation between patient preference and randomisation. I have questioned that dogma and proposed a scientifically sound consumer principle of randomisation;[2] this allows self-determination among limited randomisation ratios (such as 70/30, 50/50, and 30/70) in preference to forcing doctor or patient to choose between not randomising (absolute certainty about the preferred treatment for this patient) and the total uncertainty of equal randomisation. The fundamental principle of randomising to achieve unbiased comparison is not breached by purposely unequal treatment numbers within a randomisation stratum. Moreover, treatment effects that have been estimated unbiasedly within stratum can be compared between self-determined strata as a check on generalisation of the trial results to patients who differed in initial preference.

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2 Gore SM. The consumer principle of randomisation. *Lancet* 1994; **343**: 58.

Authors' reply

SIR—Brewin reminds us that early in the history of the modern RCT some trialists were concerned about the issue of patients' consent. But few will deny that many others argued that "it is often quite impossible to tell ill-educated and sick persons the pros and cons of a new and unknown treatment versus the orthodox and known [intervention]".[1] These doctors were convinced (*pace*, Thornton) that they were acting in their patients' best interests when they enrolled all eligible candidates without obtaining formal permission. Although the exact numbers are unknown, the change in sampling was immediately obvious. Investigators conducting RCTs when mandatory written consent arrived in the mid-1960s noticed a sharp fall in the proportion of eligible patients enrolled in these exercises.

We find it hard to accept Bradley's view of the role of randomisation in clinical trials. Our confidence in the internal validity of randomised trials is based on the laws of probability (variations in known and unknown characteristics that may bias outcomes in compared groups are distributed by chance). As we pointed out, this confidence in the distribution of confounding influences is missing when randomised and non-randomised groups are compared. With Bradley's partly randomised preference design, internal validity is retained for those patients willing to be randomised, but is absent in the comparison of patients who receive the same treatment by choice or through random allocation. The use of this design also has implications for the external validity (generalisability) of trial findings. Nevertheless, we agree with her that researchers should report recruitment procedures, and that further research into patient preferences is desirable, as McPherson also suggests. We understand Gore's concern about "absolute polarisation between patient preference and randomisation", but we doubt whether her suggestion would be acceptable to patients who have a clear preference for one treatment.

The hazards in making reliable estimates of treatment effect based on comparison between self-selected groups seem formidable. We agree with Schmoor and co-workers,[2] who noted that "inferences drawn from studies incorporating a proportion of patients without randomised treatment allocation must be regarded as qualitatively comparable to those drawn from purely observational studies". Thus we cannot agree with Bradley that the Cochrane Collaboration gives undue weight to the results of randomised trials.

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1 Armitage P. Bradford Hill and the randomised controlled trial. *Pharm Med* 1992; **6**: 23–37.
2 Schmoor C, Olschewski M, Schumacher M. Randomised and non-randomised patients in clinical trials: experiences with comprehensive cohorts studies. *Stat Med* 1996; **15**: 263–71.

Financial hijacking of conferences

SIR—Bennett (Feb 10, p 377)[1] discussed some of the problems of the ever-increasing size and number of biomedical conferences. What were originally opportunities for groups of like-minded individuals to gather and discuss new research and present their own work and ideas, seem to