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# Psychological issues in clinical trial design

by

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ABSTRACT

Randomised controlled trial (RCT) designs are widely regarded by the medical establishment as the trial design of choice, believed to offer greater internal validity than non-random trials. However, where patients have preferences among treatments to be compared, randomisation can create differences between groups in a trial.

The limitations of conventional RCTs are considered in the context of treatments for chronic conditions where patients often have strong treatment preferences. Precautions required in selection and recruitment of patients into RCTs are recommended together with strategies for evaluating any effects of preferences.

Alternative trial designs which take account of patients' and/or doctors' preferences when recruiting patients and allocating treatments are reviewed, including Brewin and Bradley's increasingly widely used partially-randomised preference trial (PRPT) design. Recommendations are made for future use of trial designs which take account of preferences and provide interpretable results of value to clinicians and patients in routine clinical practice.

## Recent Developments in Treatment Evaluation

Archie Cochrane in the early 1970s made a very important contribution to discussions about raising standards of health care when he pointed out that a major problem for our health service was that most of the health care provided had not been adequately evaluated. Treatments in widespread use may have no benefit and may even be harmful. In an important book published in 1972, Cochrane suggested that randomised controlled trials (RCTs) were of great value in improving the National Health Service (Cochrane, 1972). At that time, Cochrane had an uphill struggle in persuading doctors to allow randomisation to decide which patient would receive which treatment. Today, RCTs are widely accepted by medical researchers as the best way of evaluating treatments. Indeed some go as far to say that they are the only way of evaluating treatments. Their argument is that, since randomisation alone eliminates the selection effect of therapeutic decision making, anything short of randomisation to attribute cause to outcome is a waste of time, and certainly a poor substitute for the conventional RCT (Silverman and Altman, 1996; 1996a).

Although Cochrane died in 1988, he lives on as the figurehead of an international movement, the Cochrane Collaboration, dedicated to the systematic evaluation of treatments via methodologically sound clinical trials and systematic meta-analytic reviews of the literature. I am personally a founder member of the Cochrane Collaborative Review Group in Diabetes. There are review groups on an increasing number of medical and psychiatric conditions including stroke, perinatal care, pregnancy and childbirth, schizophrenia, and epilepsy. The Cochrane Collaboration has centres in the UK, Canada, USA, South America, the Netherlands, Scandinavia, Australia and New Zealand, and a major part of their role has been to facilitate systematic reviews by searching the literature for clinical trials. Unfortunately, so convinced have the majority been that RCTs are the best, perhaps the only, worthwhile design for clinical trials, that they have restricted their searches to RCTs. Only when RCTs have not been available in a particular field of medicine, have trials using other designs been considered. Too much is now

being expected of randomisation and there is too little attention being given to the preferences of individual patients and clinicians (Bradley, 1988, 1993, 1996). The balance needs to be redressed. Health psychologists can make an important contribution to the design of clinical trials which take account of psychological factors in a way that will sensibly and usefully inform patients and doctors who are faced with the task of choosing between treatment options. Designs are needed which take account of doctors and patients as individuals with differing beliefs, needs and priorities which can influence their attitudes and behaviour when choosing and making use of medical treatments.

Patients' views are now attracting increased interest in clinical trials with measurement of 'quality of life' issues becoming the rule rather than the exception. However, there is still some way to go to adapt the questions asked in trials and the methodologies used so that they meet the needs of individuals in the manner of good patient-centred clinical practice. We need to move on from simplistic questions about "Which treatment is best?" to questions about "Which treatment suits this patient best given the particular circumstances".

## Randomised Controlled Trials versus Preference Trial Designs

The experience of being involved with two very different trials of continuous subcutaneous insulin infusion pumps (CSII pumps) in diabetes care illustrated the pros and cons of randomised controlled trial designs and of non-random feasibility studies. In both trials; the use of CSII pumps was being compared with the use of injection regimens. One trial was a non-randomised feasibility study. About 400 patients took part in this study directed by John Ward in Sheffield (Knight, Boulton, Drury, Gamsu, Moses, Bradley and Ward, 1984). Few patients invited to participate declined to do so. About one third of patients wanted to try the pump while the rest opted for a conventional injection regimen or an intensified injection regimen (see Figure 1a for design). The second trial was a multicentre European randomised controlled cross-over trial organised by Kirsten Staehr Johansen at the World Health Organisation (WHO) Europe in

Copenhagen (Staehr Johansen, 1991). Patients recruited were those willing to use both CSII and injection treatments during the trial (see Figure 1b for design). There were two major differences between the feasibility study and the RCT. First, while the majority of patients participated in the feasibility study, only the minority (38%) took part in the RCT. Within the RCT, recruitment success varied markedly from centre to centre: fewer than 20% of those invited were randomised into the study in Paris while in Albania the figure was 70%. Secondly, there were many drop-outs from the RCT which undermined assumptions about group membership being determined randomly. Interestingly, although there was heated debate about which treatment should be used during run-in to reduce the drop-out rate in the RCT, there was no discussion about how and what patients should be told about CSII. What patients were told differed from centre to centre.

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Figure 1 about here

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In the Sheffield feasibility study, all patients were invited to an illustrated lecture on the treatments available in the study. Patients were told that “the evidence suggests that pumps control blood sugar levels better than injections". With hindsight it was clear that many patients were given the idea that the pump would control their blood sugar *for* them and would require less effort than an injection regimen. Patients most readily attracted to CSII pumps after hearing this lecture turned out to be those who were the least likely to be suited to the considerable demands of pumps. A measure of Perceived Control of Diabetes (Bradley, Brewin, Gamsu and Moses, 1984) suggested that they were looking for a medical solution that would reduce the demands on them to manage their diabetes (Bradley, Gamsu, Moses, Knight, Boulton, Drury and Ward, 1987). Sadly the pump turned out to require *more* rather than *less* effort from the patient and these patients were not prepared for this. The result was a massive increase in diabetic ketoacidosis (DKA) among pump users during the first two years of the study. Psychological variables were much better predictors of the occurrence of DKA than any of the biomedical

variables measured. In particular, those patients with less sense of personal control over their diabetes and a greater sense of medical control were more likely to develop DKA (Bradley, Gamsu, Knight, Boulton and Ward, 1986).

With the psychological measures and knowledge of what patients were told about the treatments, it was possible to understand why patients made the treatment choices they did in the feasibility study and the consequences that followed. With the RCT, only a minority of patients agreed to participate and there was little information about those who declined to participate in the trial. It was likely that those who took part did so because they thought they would prefer CSII pumps to their current injection regimen. It was not likely that they would have a preference for injections because they could have that treatment outside the trial without risk of being given a non-preferred treatment. In an Editorial in *Diabetic Medicine* (Bradley, 1988), the argument was put forward that when patients recruited into a trial have a preference for the new treatment, random allocation will actually create differences between the groups that were not there to start with. Random allocation had previously been assumed to be the best way of minimising differences between two groups of patients given two different treatments to be compared in the trial. This may be quite reasonable where patients have no strong views about which treatment would suit them best but if they do have strong views an RCT design will create problems. It will be difficult to recruit patients who have a preference for the conventional treatment and patients agreeing to participate will therefore tend to be biased in favour of the new treatment. Where the success of a treatment depends on patients' actions (even if it is only a matter of taking a tablet at certain times of day), there is scope for patients to make a preferred treatment work better than a treatment they are disappointed to receive.

### The Partially Randomised-Preference Trial (PRPT) Design

The ideas of the *Diabetic Medicine* Editorial were subsequently generalised to other areas of medicine (Brewin and Bradley, 1989; Bradley and McGee, 1994) and a means of combining the

best elements of RCTs and feasibility studies was offered in a design that has since been widely referred to as a partially randomised-preference trial (PRPT) design (Brewin and Bradley, 1989; Bradley, 1993). In the PRPT design (see Figure 2) patients are told about the treatment options and asked if they have a strong preference for one or other of the treatments to be compared. If they have a strong preference they are allocated to their preferred treatment (groups 1 or 2 in Figure 2). If they have no preference they are allocated at random (to groups 3 or 4 in Figure 2).Patients who prefer the standard treatment are accommodated in group 2 of the PRPT design while these patients would be unlikely to participate in a conventional RCT. Patients who prefer the new treatment, and are allocated to group 1 in the PRPT in Figure 2, may well have been included in an RCT if it was their only chance of obtaining their preferred treatment. Inclusion of patients preferring the new treatment while those with preferences for the standard treatment decline to participate in an RCT, will bias the sample recruited into an RCT in favour of the new treatment. If everyone recruited into a PRPT turns out to have a strong preference, a feasibility study will result. If no one has a preference, an RCT will result but it will differ from a conventional RCT because motivational factors will have been explicitly considered and controlled for.

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Figure 2 about here

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It may be that while some patients express a preference for one of the treatments, no one prefers the other treatment. It is important to pilot the information given to patients to see what effects it is likely to have on recruitment. It may be that the presentation of information is leading to the bias in apparent preferences which could be equalised by modifying the way the information is presented. This is empirically testable. As well as offering a purer form of RCT within the partially-randomised design, the PRPT design offers the advantages of feasibility studies (notably the acceptability to patients and hence the high proportion of patients recruited).

The PRPT design also offers the opportunity to compare the results obtained by groups where motivational factors can be assumed to be similar (Groups 3 and 4) and the results of groups where motivational factors differ (groups 1 versus 3 and groups 2 versus 4). Separate comparisons can be made to determine the extent to which motivational factors influence outcomes.

The first published trial using the Brewin and Bradley PRPT design was reported by the Health Services Research Group in Aberdeen (Henshaw, Naji, Russel and Templeton, 1993). The trial compared medical abortion with surgical vacuum aspiration. The response rate for the PRPT design was excellent with only 3 of 373 women invited to participate declining to do so. The results depended on women's preferences and gestation duration. The authors recommended that women with a preference should have their choice. Women of 50-63 days' gestation, without a preference, were likely to find vacuum aspiration more acceptable. It was commented that

> "A simple randomised (or entirely pragmatic) trial would not have yielded these results. Hence, the patient centred partially randomised design advocated by Brewin and Bradley may be a useful tool in pragmatic research in populations characterised by an unwillingness to comply with all treatments under investigation." (Henshaw et al., 1993, p.717).

Thus Henshaw and colleagues saw the PRPT design as a way of overcoming the difficulties of recruitment into RCTs where patients have to be prepared to accept any of the treatments under study. The researchers adopted the design for pragmatic rather than for scientific reasons. However, there are powerful scientific reasons for not using an RCT when patients have preferences even if it is possible to persuade patients to take part. A particularly important feature of the PRPT is that, in selecting out the patients with preferences for study in separate

groups, the sample to be randomised is in 'equipoise'.

## Equipoise

The concept of equipoise has been used predominantly in discussions of the ethics of trials rather than in debates about the scientific value of trials. However, it is argued here that equipoise is also highly relevant to the science of trials.

*Clinician Equipoise*

Freedman (1987) defined two forms of clinician equipoise: theoretical equipoise and clinical equipoise. Those were subsequently relabelled as individual and collective equipoise respectively (Lilford and Jackson, 1995). Theoretical or individual equipoise arises when the available 'evidence' is balanced in favour or against each of the two treatments to be studied. The 'evidence' can include clinical observation of individual patients and individuals' experience of symptoms, rumour and speculation as well as published research results. In practice, such equipoise is too fragile to be maintained as the balance is too easily disturbed by each new data point collected and every side effect mentioned as well as by the published results of trials. Clinical or collective equipoise, on the other hand, arises when there is no consensus in the expert community about which is the better treatment. With each of these definitions of equipoise, the definition is in terms of clinician preferences - either an individual clinician's preferences or the preferences of the community of clinicians. Freedman suggested that

> "A state of clinical equipoise is consistent with a decided treatment preference on the part of the investigators. They must simply recognize that their less-favoured treatment is preferred by colleagues whom they consider to be responsible and competent." (Freedman, 1987, p.144).

Under these circumstances a trial is ethical even if an individual clinician has preferences for one of the treatments in the trial. However, recent evidence suggests that trialists ignore clinician

preferences at their peril. This point is returned to below.

*Patient Equipoise*

The importance of patient equipoise, which to date seems to have been overlooked, needs now to be recognised. Patient equipoise arises when individual informed patients have no clear preference for any of the treatments available. If patients are not in equipoise, we cannot depend on randomisation to do what it is intended to do - that is to create two similar groups. Confidence in the ability of randomisation to create comparable groups regardless of patients' preferences is misplaced. Randomisation can only work to produce comparable groups if patients have no strong preferences. In order to achieve patient equipoise there are two crucial steps which need to be taken when recruiting patients into trials. First, patients need to be well informed about the treatments on offer and, secondly, their preferences, if any, need to be elicited.

## Recruitment Procedures

Rarely are the recruitment procedures described adequately in journal reports of trials. This problem can result from journal editors' space-saving cuts as well as from inadequate accounts by authors. Henshaw et al's paper reporting on the PRPT design comparing medical versus surgical abortion included little information about recruitment procedures (Henshaw et al., 1993). Enquiry revealed that the procedure used had confused the issue of eliciting preference by failing to ensure equipoise in the randomised groups (Henshaw, 1994: communication during a workshop on patient preference designs at the UK Cochrane Centre, April 1994 (Silverman, 1994)). Examination of the information sheet given to patients in this trial showed that the trial was presented to patients initially as if it were a conventional RCT. Only if the patients refused to participate did the clinician/researcher tell them that they could have their preferred treatment. What this means is that the randomised component of the trial may well have included some patients with preferences. Further enquiry was made about whether the patients understood that the new medical treatment was only available within the trial or whether they thought that they

could have either treatment without participating in the trial. It was revealed that the obstetrician who recruited the patients into the trial did not address these issues and did not know what patients believed about the availability of treatments. It may be that some patients decided to participate in what they believed to be an RCT because they thought they would prefer the new medical treatment and believed that participation in the trial was the only way it could be obtained. However, in practice, the results showed that although the two preference .groups (equivalent to groups 1 and 2 in Figure 2) were satisfied with the procedures chosen, the randomised groups (groups 3 and 4 in Figure 2) tended to be more satisfied with the surgical procedure. The results do not suggest that the randomised groups included a preponderance of women preferring the medical treatment to start with, and we know that they did not prefer the medical treatment at the finish. If they had preferred the medical treatment and thought they could only have this treatment within the trial, there would have been women randomised to surgery who would have preferred medical treatment, and the resulting outcomes for surgery may well have been impaired compared with the results expected if equipoised patients only had been included.

The Aberdeen group has gone on to use the partially randomised preference trial in another context comparing new surgical versus medical treatments for menorrhagia (Cooper and Grant, personal communication). In this trial a more appropriate recruitment strategy was adopted. Cooper and colleagues did not wait until patients refused to participate in an RCT before telling them they could have their preferred treatment but instead asked in the information sheet for any preferences to be declared. In addition, Cooper et al. compared the methodology of the PRPT design with that of a conventional RCT randomising 273 women with menorrhagia to a PRPT design or to an RCT. As was found in the previous PRPT by Henshaw and colleagues, the PRPT recruited virtually all patients, 67% of whom were prepared to have their treatment determined by randomisation. The RCT recruited only 70% of patients invited. A questionnaire for the 30% refusing to participate in the RCT, indicated that most had strong preferences and declined to

participate as they could have their preferred treatment outside the trial. Because in this study, they could have their preferences outside the trial, the randomised sample is likely to be in equipoise even in the RCT and the results obtained from the randomised groups of the two trial designs would not be expected to differ. Although in this instance the randomised groups in the RCT were likely to be in equipoise and the results, therefore, readily interpretable, without the PRPT component of the trial we would not know anything about how the 30% who declined randomisation would respond to treatment. The PRPT follows them up and provides opportunities for comparisons with the additional groups included.

Where a preferred new treatment is not available outside the trial, I would predict that the results of a PRPT would be more likely to differ from those of a conventional RCT. Then the refusers who preferred the new treatment would be likely to participate in order to have the chance of their preferred treatment. Approximately half of them would be disappointed when randomised to the standard treatment. The disappointed patients would be more likely to stop following the standard treatment recommendations and do less well, thereby exaggerating the advantages of the new treatment. The extent of the exaggeration will depend on the proportion of patients disappointed. In studies where preferences are strongly in favour of a new treatment unobtainable outside the trial, an RCT may produce results which are misleading.

### Interpreting the Findings of RCTs Involving Patients with Preferences

One recent trial measuring psychological outcomes demonstrates the importance of careful interpretation of clinical trial results when patients tend to prefer a treatment not available outside the trial. The trial compared a new fast-acting insulin ('lispro' - designed to be taken immediately before a meal) with standard soluble insulin (usually recommended to be injected 30 minutes prior to a meal) (Janes, Bradley and Rees, 1997). In practice, the recommendation to inject standard soluble insulin 30 minutes pre-meal is difficult to follow and carries with it an increased risk of hypoglycaemia, a risk that is increased further if the meal is unexpectedly delayed. Many

find that they cannot follow the recommendation or choose not to do so in order to avoid hypoglycaemia. Others attempt to follow the recommendation with varying degrees of success and inconvenience. The patients recruited into this particular trial were those who had been trying to inject 30 minutes prior to meals. Ninety-seven patients with insulin-dependent diabetes (IDDM) were recruited into a 6 month multi-centre randomised cross-over trial comparing insulin (lispro) injected immediately pre-meal versus standard soluble insulin injected 30 minutes pre-meal. The trial was an 'open-label' trial with patients and their doctors being fully informed about the insulins they were using.

Outcome variables included patients' satisfaction with their treatment measured by the Diabetes Treatment Satisfaction Questionnaire (DTSQ) (see Bradley, 1994 for review) and Depression, Anxiety, Energy, and Positive Well-being measured by the Well-being Questionnaire (W-BQ) (see Bradley, 1994a for review). Improvements in Treatment Satisfaction scores were expected with lispro, particularly in terms of increased convenience and flexibility (two of the eight items in the DTSQ). Improvements (rather than deterioration) were anticipated on the W-BQ subscales though changes on the diabetes-specific DTSQ were thought more likely than changes in more general well-being. Results showed significant treatment differences ($p<0.01$), all favouring lispro, as expected for the DTSQ total score and for the single item concerned with treatment convenience. There were also significant treatment differences ($p<0.01$) favouring lispro for the W-BQ total score, and for three of the W-BQ's four subscales which measured depression, anxiety and energy. These results, overwhelmingly in favour of lispro, were obtained by combining the treatment periods for the energy scores (where no carry-over effect was apparent) and by analysing the first treatment period only for the DTSQ, Depression and Anxiety scores for which significant carry-over effects were found by the study statistician who then followed accepted practice and excluded data from the second part of the study following the cross-over. However, when we look in more detail at the patterns of results within this cross-over design we

see an interesting and more complex picture.

The DTSQ results are shown in Figure 3a. Because patients were already quite satisfied with their standard soluble insulin used at baseline, the advantages of lispro were most clearly seen when patients who had tried lispro, went back to standard soluble insulin and their satisfaction with treatment fell markedly. Similar patterns of results were seen in the WHO cross-over study of CSII pumps versus injections where satisfaction with treatment plummeted when patients returned to injections following a period of CSII use (Bradley, 1994). A parallel groups design would have underestimated the effect unless a change version of the satisfaction questionnaire could have been used at follow-up alongside the status version used here (Bradley, 1996a). In a cross-over trial, there is a danger that the effect is dismissed inappropriately as a "carry-over" or "order" effect and only the first phase of the study considered - thereby eliminating the most dramatic change. If data from the second treatment period had been excluded, as the study statistician was initially inclined to do, the benefits of lispro experienced by these patients would have been underestimated.

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Figure 3 about here

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The DTSQ is picking up a recognisable phenomenon here - that people make the best of things when they think they have the best available and only appreciate or acknowledge the inconveniences and discomforts of the standard when they have found something better.

The improvement in Depression scores with lispro, shown in Figure 3b, was as much due to increased Depression scores in the standard soluble first group as to a decrease in Depression scores in the lispro first group. This looks like a disappointment effect facilitated by differences between groups in baseline scores. The same pattern was apparent for Anxiety with significant

carry-over effects in each case. The improvements in Energy scores with lispro were seen before and after cross over, were not attributable to deterioration in the control condition and may well reflect metabolic benefits of lispro. However, the pattern of results for Depression and Anxiety is probably dependent on the patients recruited being those with a strong preference for lispro. Certainly this suggestion is supported by data from the end of the trial where 83% of patients elected to continue with lispro. Here the significant difference in Depression scores favouring lispro is due as much to patients becoming more depressed following allocation to the control group as it is to patients becoming less depressed following allocation to lispro. Within-group decreases in Depression and Anxiety in lispro-treated patients were not significant in themselves but only became so when contrasted with the increased Depression and Anxiety scores of the control group. There are many examples of such effects published in the literature which are widely accepted at face value. For example, Surwit and Feinglos's (1983) trial of the effects of relaxation training on glucose tolerance in people with NIDDM showed improvements in the glucose tolerance of the relaxation group relative to the control group who were hospitalised but not given training and whose glucose tolerance deteriorated.

Thus, patients disappointed at being allocated to a non-preferred control treatment may show deteriorations in outcomes which further augment the benefits of the preferred treatments over and above that augmentation already possible as a result of recruitment of patients preferring the new treatment. These two phenomena may lead to overestimation and overgeneralisation of the advantages of a new treatment. This is not to say that the new treatment does not have advantages, but proper evaluation of those advantages requires comparison with an appropriate control group uncontaminated by disappointment effects, and consideration of the representativeness of the trial sample and the generalisability to the patient population as a whole. The great majority of the patients recruited into the lispro trial described here was clearly more satisfied with lispro than with standard soluble insulin. It may or may not be the case that the greater satisfaction with lispro would be apparent in patients who would not have agreed to

participate in this trial because they were satisfied with standard soluble and saw no reason to change. Patients initially reluctant to try lispro may be recruited into subsequent trials inspired by the reports of patients' experiences in previous trials. The extent to which the initial results can be generalised to the wider population of insulin-treated patients could then be estimated with greater accuracy.

If patients with strong preferences are given their preferred treatment we are likely to optimise their psychological outcomes, increasing their satisfaction and perhaps also their psychological well-being. In addition, the biomedical outcomes are likely to be improved when patients' preferences are matched to treatment, especially where the biomedical outcomes depend on patients' appropriate use of the treatment (as is the case with insulin). Biomedical results from the lispro trials are encouraging and indicate a reduction in severe hypoglycaemia while maintaining comparable levels of HbA1 (Schmitt, Symanowski, Holleman, Rees, Rottiers and Anderson, 1996).

### Doctor Preferences and their Influence on Clinical Trials

This paper has so far focused on the importance of patients' preferences. Doctors may also have strong views about which treatment is most appropriate for their patients and such preferences can also influence outcomes. There has been considerable concern amongst the Cochrane collaborators about the increasingly publicised problem of doctors circumventing randomisation (Schulz, 1995). Schulz recounted a range of methods used by clinicians involved in trials to subvert the randomisation process. Methods included: holding envelopes containing group allocation up to X-ray viewing lights to see which group the next patient would be allocated to before deciding whether to recruit a patient and rifling the files of the principal investigator to find the sequence of group allocation. Unfortunately no enquiry was made about why the clinicians did this but instead Schulz assumed that "Randomised controlled trials appear to annoy human nature". The reasons are, however, important in determining the consequences. When the

reasons for subversion relate to the clinical state of the patient, trial outcomes are likely to be affected. When reasons for subversion are unrelated (e.g., a junior doctor needing more experience of vaginal hysterectomies reassigning women randomised to abdominal hysterectomy to vaginal hysterectomy) trial outcomes are less likely to be influenced.

The Cochrane Collaboration has been particularly concerned about the adequacy of allocation concealment because inadequate allocation concealment has been associated with larger treatment effects than have been found in trials where adequate allocation concealment was reported. Odds ratios increased on average by 30 - 40% with inadequate concealment (Schulz, Chalmers, Hayes and Altman, 1995).

It is widely assumed that odds ratios are exaggerated with inadequate concealment, and that adequate concealment leads to a more correct estimate of effects. However, it may well be that doctors and patients are better able to match preferences and needs to the treatments available if they subvert the randomisation process and can achieve better outcomes as a result. True randomisation with adequate concealment may well diminish outcomes where patients and/or their doctors have reasons to believe that one treatment in a trial will be more suitable for a particular individual than the other treatment. The poorer outcomes associated with randomisation may be seen as the result of thwarted preferences which bias the results in a negative direction. We want to optimise the outcomes; matching patients' preferences to treatments is one important way of doing this and matching doctors' preferences to treatments may be another.

Korn and Baumrind (1991) recognised that doctors often have views about which treatment would best suit a patient, and that doctors may exclude a patient from an RCT rather than risk their being assigned to the doctor's non-preferred treatment. Such preferences may vary from doctor to doctor and create differences in outcomes in different centres as well as slowing

recruitment into trials. Korn and Baumrind suggested a trial design for taking account of doctors' preferences where randomisation is only offered to a patient when a panel of doctors disagree about which treatment is preferable for that patient. The patient is assigned to one of the doctors expressing a preference for the treatment to which the patient was subsequently randomised. Where all are agreed on the preferred treatment for a patient, that patient is given that doctor-preferred treatment. A major problem with this design, which has been discussed in more detail elsewhere (Bradley, 1993), is that patients' preferences are nowhere considered and it is assumed that patients will rely on the advice of their physicians. Patients may indeed rely heavily on their doctor's advice in circumstances where treatments are doctor-administered over a short time period with few implications for patients' life-styles and where patients have little knowledge of their condition or the treatment options. However, these circumstances do not usually apply in the case of management of chronic disorders such as diabetes or renal failure. Interestingly, in a recent study of decisions concerning dental extraction by Baumrind, Korn, Boyd and Maxwell (1996), agreement among clinicians was higher than the authors had anticipated. In almost two thirds of the 148 cases considered, all five clinicians involved were in agreement about whether extraction or non-extraction was the preferred method of treatment. The choice of clinicians recruited into such a study is likely to be crucial in determining the degree of agreement between them and it is not clear how a panel of clinicians might best be selected. However, in any centre involved in a clinical trial, the views of the clinicians involved, whether in agreement with each other or not, may well have important influences on the conduct and outcomes of the trial.

### Interim Steps Towards More Creative Clinical Trial Design

There is a need for more creative use of clinical trials where patient and doctor preferences are considered. It can often be very difficult to persuade medical colleagues to shift from their conviction that a conventional RCT is the best design. An interim step between a conventional RCT and a PRPT is to ask participants in the trial about their preferences and analyse the trial results taking initial preferences of patients and their doctors into account. Torgerson, Klaber-

Moffet and Russell (1996) have reported a trial comparing an exercise programme for back pain with conventional general practitioner management. The authors recognised that patients' preferences may be an important prognostic variable but believed that they would have more 'robust statistical comparisons' if they used only randomised groups and took the decision to randomise patients to a less preferred treatment rather than using a PRPT design. Of the 97 patients randomised into the trial only one patient preferred the standard treatment while 58 preferred the exercise programme and 38 had no strong preference. The authors did not tell us how many patients declined to participate (a subset of patients who may well have marked preferences for the standard treatment) and seem unconcerned about the biased nature of a sample where the vast majority of patients recruited prefer the new exercise treatment. They argued that:

> "the results of this trial will still be generalisable to normal clinical practice as patients unwilling to participate in an exercise programme would be unlikely to comply with such a programme. Thus the absence of patients preferring standard treatment is more pragmatic, or true to real practice, than if such patients had been encouraged to take part in the trial." (Torgerson et al., 1996, p.196).

While it may be true that to ignore patients who do not wish to try the new treatment is more akin to real practice than to encourage them to take part against their wishes, in the real clinical world these patients cannot simply be ignored. Furthermore, by excluding this subset of patients with a preference for the standard treatment, the authors do not allow us the opportunity of discovering that such patients may actually do better with the standard treatment than patients who preferred exercise or those who had no preferences. Indeed patients who prefer standard treatment may even do better with that treatment than other groups treated with the exercise programme. Torgerson and colleagues were concerned that the patients who preferred the exercise programme, when compared with those who had no preferences, had a higher belief in the

effectiveness of the new treatment, tended to have worse back pain, back pain of shorter duration and more GP home visits. Had they used a PRPT design they would indeed have recruited patients into the group preferring the exercise treatment who differed from those randomised into treatment groups. They were reassured that, when they randomly allocated all the patients regardless of their preferences, they found no differences between the two groups in the baseline variables measured. However, this is little reason for confidence in the RCT design when 34 of the 52 randomised into the standard treatment had expressed a preference for the exercise treatment while none of the 45 randomised into the exercise treatment had a preference for the standard treatment. Thus none of those in the exercise treatment group but 65% of the standard treatment group will be disappointed with the treatment allocated at randomisation.

Torgerson and colleagues have yet to report the analyses of the outcomes of their trial and it will be interesting to see how the outcomes of those without preferences compare with the outcomes of those who preferred the exercise treatment. Unfortunately we will not know the fate of those who preferred the standard treatment and declined to participate but we can look forward to hearing how many such patients there were and which, if any, patients dropped out following randomisation. We will then be in a much better position to judge the suitability of the design and the robustness of the comparisons made.

Measurement of preferences in patients who decline to participate in an RCT, as well as in those who do participate, allows us better to judge the generalisability of the trial findings, although not to the extent possible with a PRPT which can accommodate everyone invited and follow them up. As more researchers take account of the effects of patient preferences on outcomes when analysing the results of RCTs, the case for using a PRPT will become clearer.

**Summary of Recommendations**

Several recommendations can be made.

1) The influence of recruitment procedures on outcomes needs to be recognised and given active consideration in designing trials.

2) Blind faith in randomisation needs to be replaced with a careful weighing up of the advantages and disadvantages of randomisation and consideration of the possibility that a partially randomised preference trial may be preferable to a conventional randomised controlled trial.

3) If patients are to be randomised, they need clear, accurate information about the available treatments, and steps should be taken to ensure that patients are equally willing to use either treatment (i.e. are in equipoise) before they are randomised. This can be achieved by ensuring that patients with preferences can have their preferred treatment within or outside the trial.

4) Valuable information about the outcomes for patients who are particularly motivated towards one or other of the treatments can be gathered, and the results can be generalised more successfully when these patients are included within a PRPT design.

5) Health psychologists have an important role to play in contributing to the design, analysis and interpretation of clinical trials and to the work of the Cochrane Collaboration synthesising the results of trials. Health psychologists are especially well placed to contribute to the development of methods of taking account of doctor and patient preferences and investigating the origins and effects of those preferences with a view to understanding how best to help patients choose their treatments to achieve optimum medical as well as psychological outcomes for the individuals concerned.

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**Figure 1. a) Non-randomised and b) Randomised trials of CSII pumps versus injection therapy.**

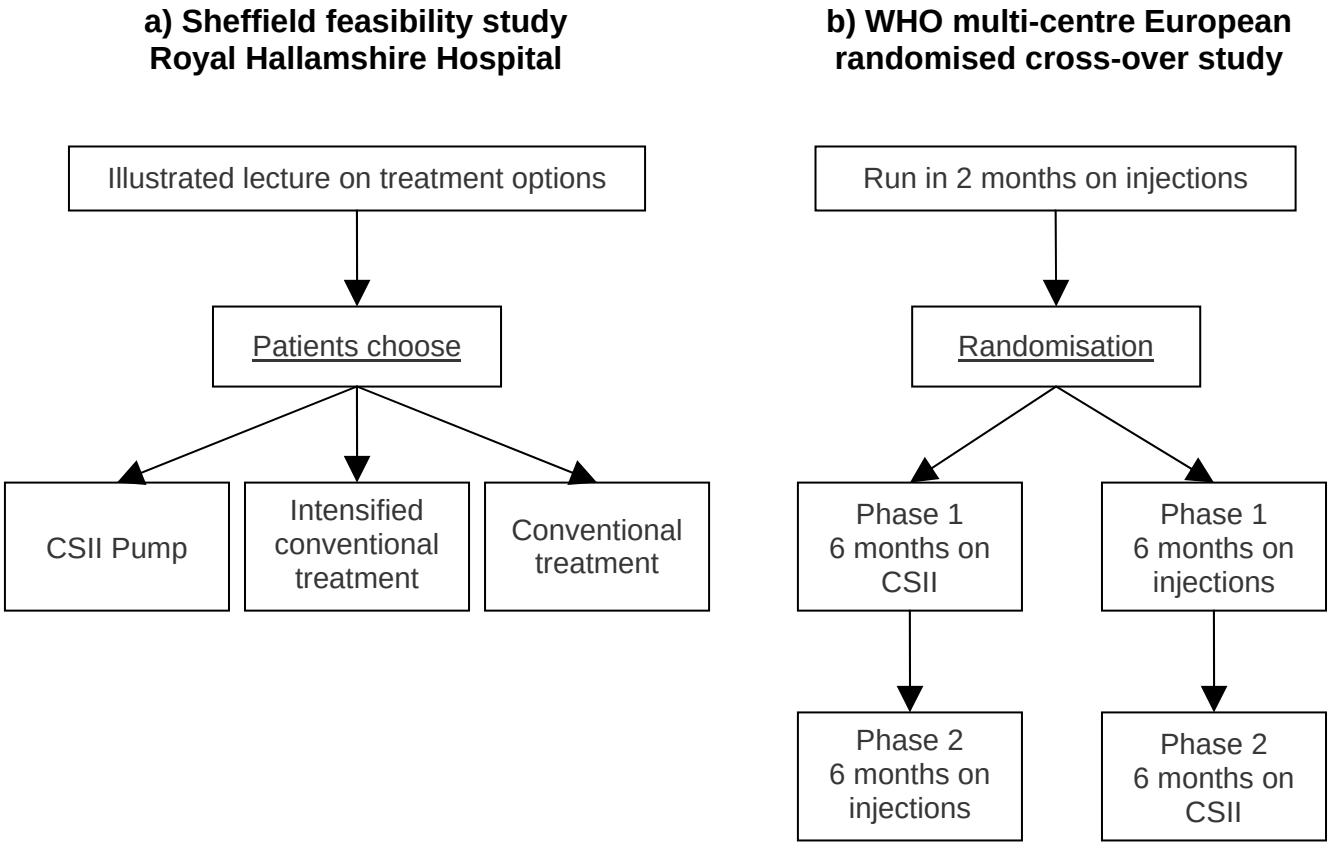


**Figure 2. Partially randomised-preference trial design (Brewin and Bradley, 1989).**

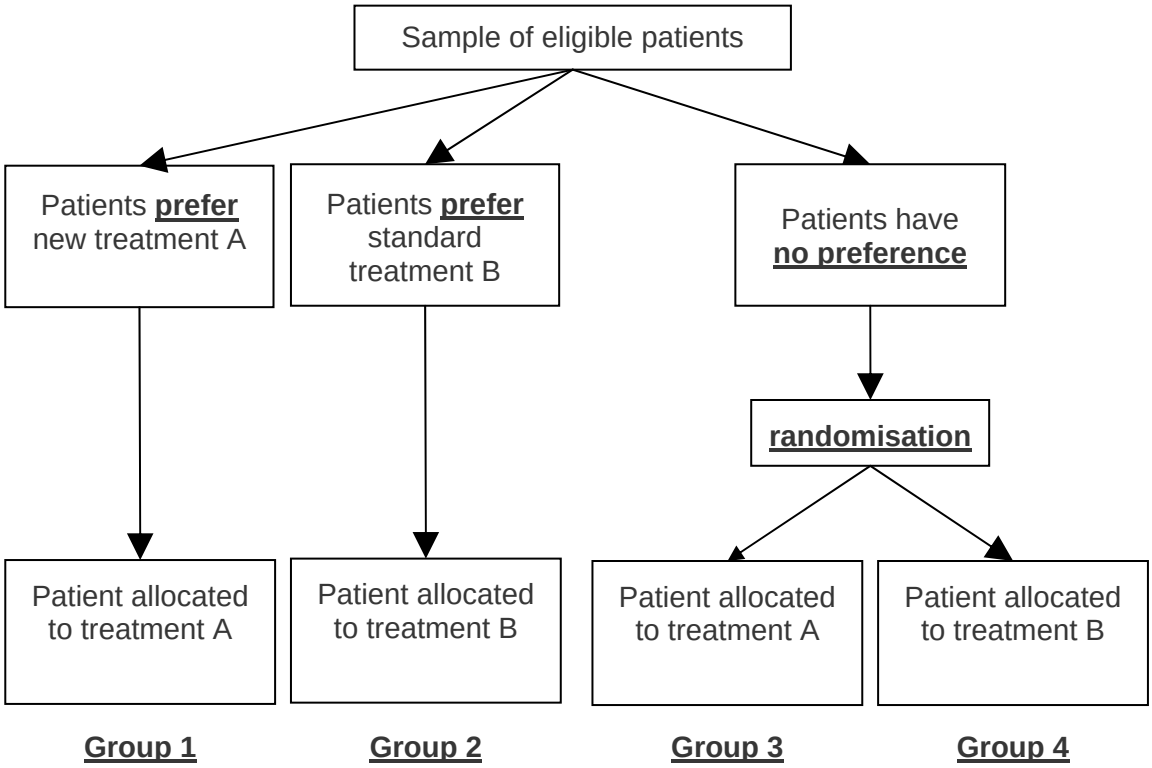
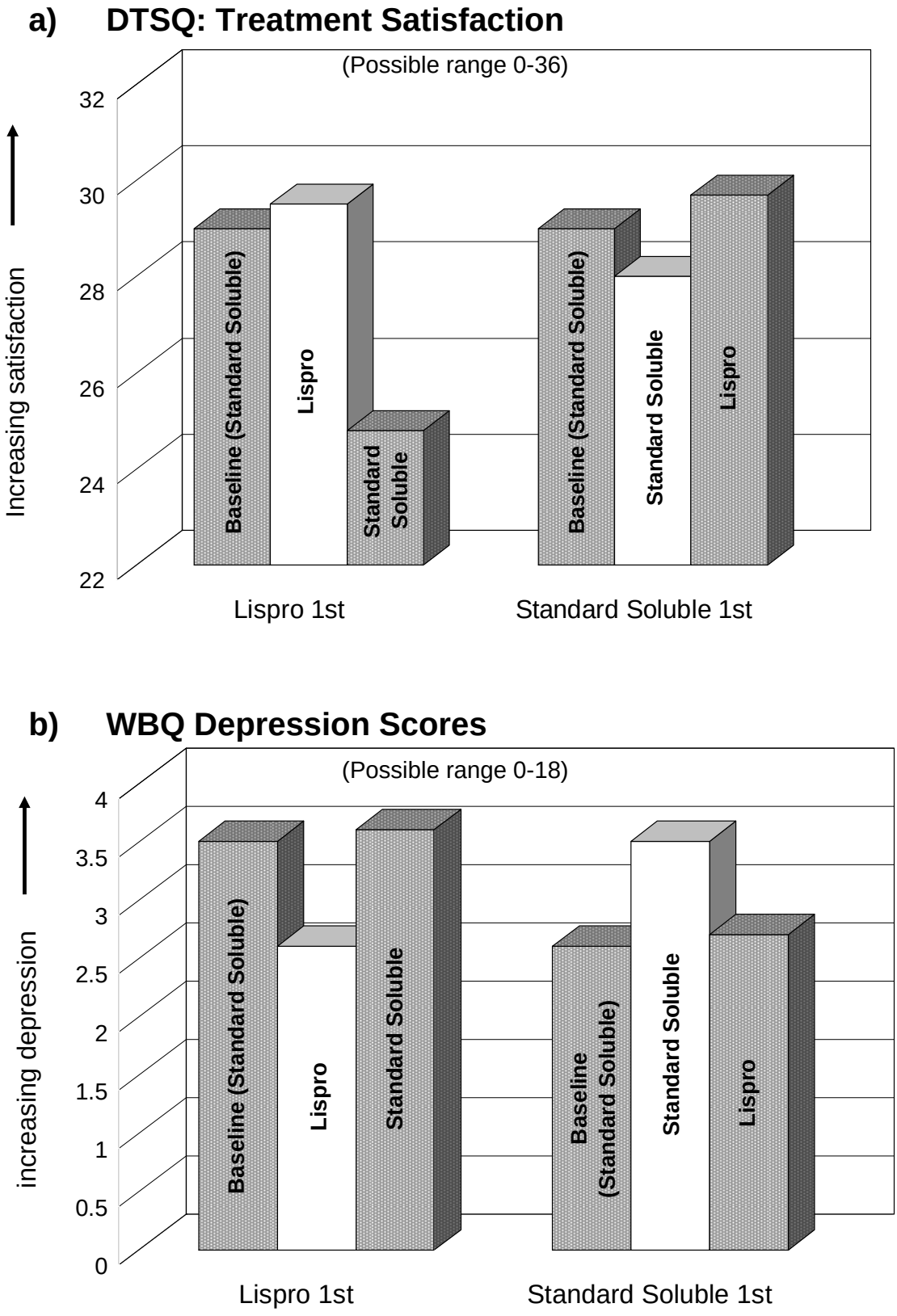


**Figure 3. Randomised cross-over trial of insulin lispro versus standard soluble insulin.**



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