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PARTIALLY RANDOMIZED PREFERENCE TRIAL DESIGN

Partially randomized preference trials (PRPTs), using Brewin and Bradley's design, are a product of combining the best elements of randomized controlled trials (RCTs), which involve random allocation of different treatments to willing patients, and feasibility studies, in which patients choose their preferred treatment. PRPTs give patients, who are recruited into a clinical trial, the option to choose their preferred method of treatment, and if the patients have no strong motivation towards a specific treatment, they are asked if they will agree to random allocation to one or other treatment method. All patients recruited into the PRPT need to be given clear, accurate, and detailed information about what the treatments to be offered in the trial involve. They can then make an informed decision when given the opportunity in the PRPT to choose a preferred method of treatment. PRPTs can be used to evaluate many different types of treatment including medical treatment, psychological treatment, and dental treatment, or a combination of treatment types, for example, drug versus psychological treatment for depression.

This entry first details the structure of a PRPT and variations of the structure. Next, this entry discusses validity (external and internal), the acceptability of PRPT to patients, and PRPTs' advantages and limitations. Last, this entry describes the appropriate implementation of PRPTs.

Structure

In a PRPT comparing two treatments, there are potentially four separate groups of patients,

each receiving one of the two treatments, usually an established treatment and a new treatment. Patients are informed about the two treatments being compared and asked if they have a strong preference. Patients who have strong preferences for one treatment over another are allocated to a group in which they can have their preferred method of treatment. In Figure 1, patients who are particularly motivated towards the new treatment are allocated to Group 1, and patients who would prefer to use an established method of treatment are allocated to Group 2. Patients who have no strong preference and are equally prepared to use either treatment are said to be in equipoise and, with their consent, have one or other treatment type assigned randomly and are thereby allocated to either Group 3 or Group 4.

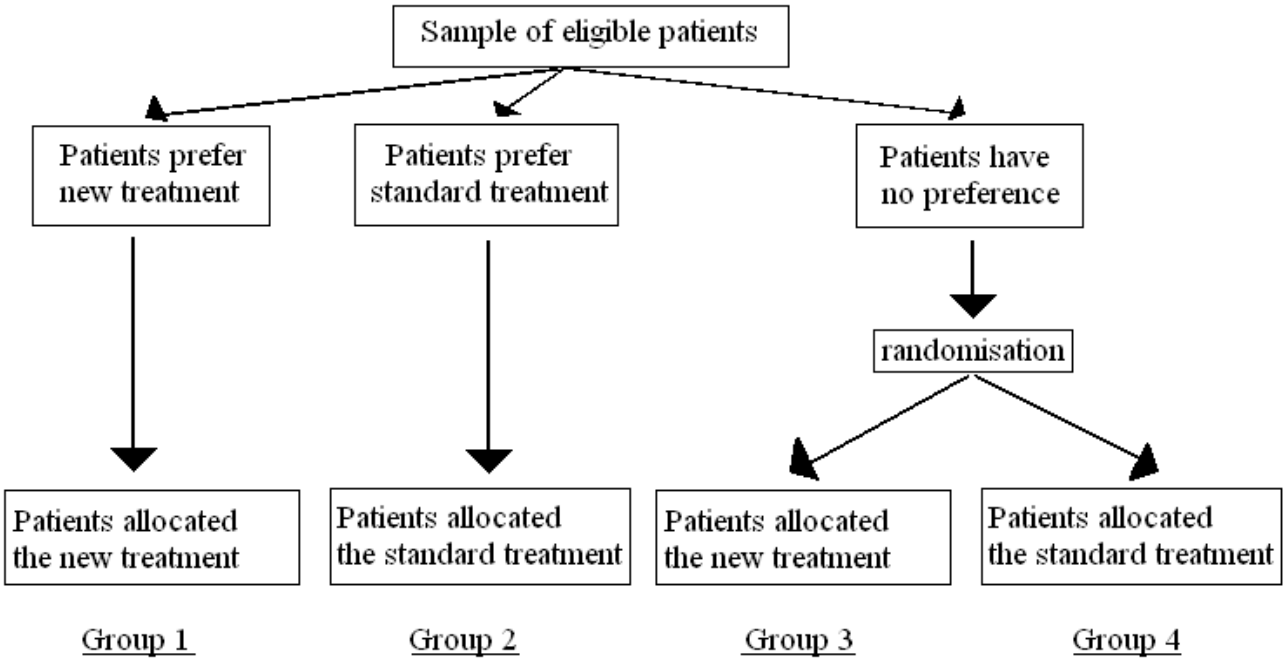

Figure 1. The Structure of a Partially Randomized Preference Trial (PRPT)

Variations on the Structure

Three-group trials may result if no one has a strong preference for one of the treatments. A

very small number of patients in one of the preference groups (Groups 1 or 2 in Figure 1) may not be analyzable statistically but will still serve an important purpose in removing those with preferences from Groups 3 and 4, where randomization to nonpreferred treatment would lead to disappointment.

If all the patients who are recruited into the PRPT have a strong preference, a feasibility study will result where all patients chose their treatment, and if no recruit have a strong preference, an RCT will result. However, if an RCT results from patients not having a preference for a particular treatment offered, it will differ from that of many conventional RCTs as motivational factors will not distort outcomes. In a conventional RCT, some patients may agree to randomization with the hope of obtaining a new and/or otherwise inaccessible therapy. Patients who think they would prefer a new treatment (those who are allocated to Group 1 in a PRPT) may have been included in an RCT if the new treatment was unavailable outside the trial and participation in the trial was their only way of obtaining their preferred method of treatment. However, RCT participants are asked to accept any of the health care options being compared. Inclusion of patients preferring the new treatment over a standard treatment will bias the RCT sample in favor of the new treatment; those with preferences for the standard treatment are more likely to decline to participate in an RCT as they can usually obtain their preferred treatment outside the trial. The RCT sample recruited will be randomized to two groups. When preferences for the new treatment are marked, one group will contain participants who are pleased to receive the new treatment whereas the other group will contain individuals who are disappointed that they have not been allocated to the new treatment (as demonstrated empirically by Feine and colleagues in 1998 and discussed by Bradley in a commentary the following year). When the majority of recruits have a preference for the new treatment, an RCT creates groups that have been allocated at random but which differ in respect to motivation to use the treatment assigned. The control group of

participants who have been randomized to the standard treatment will contain patients who are disappointed with the treatment allocation and therefore will be more likely to drop out of the trial. They may also be less likely to follow the treatment recommendations and do less well with the treatment than they would have done if motivated to use that treatment. If disappointed patients drop out of the control group, outcomes of the control treatment will be artificially improved, minimizing any advantages of the new treatment. However, if such poorly motivated patients remain in the control group, outcomes will be worsened, thereby exaggerating the advantages of the new treatment.

External Validity

People who refuse to take part in an RCT are more likely to have strong preferences, and some participants may have strong opinions regarding the relative acceptability of the treatments being compared. People refusing to take part in an RCT because they do not want to risk being randomly allocated to a nonpreferred treatment are more likely to take part in a PRPT. Few patients invited to participate in PRPTs decline to do so (e.g., only 3 of 373 women invited declined to participate in Henshaw and colleagues' 1993 study using the PRPT design). Participants who accept an invitation for an RCT may be a minority of those invited—sometimes fewer than 20%. Within RCTs, recruitment success can vary markedly from center to center as in the World Health Organisation trial of continuous subcutaneous insulin infusion pumps versus intensified injection regimens for type 1 diabetes in the early 1980s, where recruitment ranged from 70% in Albania to 20% in Paris. An RCT may fail to recruit patients who prefer a treatment available outside the trial, and for those who are recruited, randomization may create differences between groups; one being disappointed whereas the other is pleased with the treatment allocated at random. Patients recruited to a PRPT, on the other hand, are likely to be the vast majority of those invited, and the results

obtained will therefore be more generalizable to the population of eligible patients. Patient preferences act to reduce the recruitment of patients into RCTs (as patients fear randomization will allocate a nonpreferred treatment) and thus reduce external validity of RCTs. External validity is improved by using a PRPT design, where patients know any strong preference will be met, and hence recruitment is usually close to 100%.

Internal Validity

Not only is recruitment success greater in PRPTs compared with RCTs, but dropout rates of PRPTs are also lower in both the randomized and preference arms than are commonly found in RCTs. As more participants drop out of RCTs, the randomization process is increasingly undermined and the groups are less comparable. With PRPTs, the randomized groups have been cleared of preferences prior to randomization, and the preference groups, being self-selected anyway, are not threatened by any few dropouts that may occur.

The importance of PRPTs and patient choice of their treatment are especially apparent when considering the best treatment for chronic illnesses, such as diabetes, where patient motivation is essential and factors such as the convenience and flexibility of treatment regimens can dramatically improve quality of life as seen in the DAFNE (Dose Adjustment for Normal Eating) trial. Motivation is more likely to influence outcome when there is a greater need for patient participation in their treatment, which may involve diet adjustment, self-monitoring and self-medication regimens. When patients play such an active role in treatments and treatment impacts on lifestyle, results may be misleading if conclusions are drawn from patients who were allocated to a method of treatment they did not want (i.e., in many RCTs). Psychological and biomedical outcomes of treatment are likely to be improved when patients' preferences are matched to treatment, especially when the biomedical outcomes of the treatment are dependent upon participative interventions.

Acceptability to Patients

The PRPT method improves treatment outcomes by increasing the chances of meeting the needs of individual patients by establishing which treatment is most suitable for a particular patient in his or her individual circumstances. Differing needs, priorities and motivation are variables that can influence individual patient choices for medical and other treatments. There are also demographic, clinical and biochemical variables which may influence which type of treatment is best suited to different patient subgroups.

People who design clinical trials are increasingly showing greater interest in patients' views and the impact of treatments on quality of life and other patient-reported outcomes. Such outcomes are usually facilitated by matching preferences with treatment. While initially the PRPT was seen as a compromise to be used when many patients could not be persuaded to accept randomization to treatments about which they had strong views, now the PRPT is more often recognized as the design of choice, superior to an RCT when patients have strong preferences, and superior to an entirely unrandomized feasibility study when at least some patients can be randomized without risk of disappointment.

Advantages of PRPTs Compared With Feasibility Studies

In feasibility studies, patients chose their own method of treatment from two or more options offered. Various physiological, psychosocial, demographic, and other characteristics of patients can affect the type of treatment that individual patients opt for and can therefore affect treatment outcomes and conclusions drawn from the trial. For example, in an obesity trial comparing a drug treatment and a diet treatment, patients who choose the drug treatment may do so because they have tried many diets and have failed to lose weight by dieting, whereas individuals who opt for the diet treatment may not have tried to diet before and may

therefore anticipate more success. Such psychosocial factors are likely to influence the individuals' motivation to use a particular treatment method from the outset of treatment. Individual differences in psychosocial factors may have a marked effect on the success of each treatment for an individual patient. The motivation to follow the treatment recommendations by patients who opt for the diet treatment would be greater than that of those individuals who had little faith in dieting. This motivational effect would enhance the advantages of both treatments in a self-selected sample. However, it is difficult to draw conclusions from feasibility studies about the value of treatments to patients who have no preferences. By interviewing patients and/or eliciting questionnaire data, the reasons patients have for choosing a particular treatment can be determined in both feasibility studies and PRPTs. However, the randomized subgroups in PRPTs allow for the treatments to be compared in groups where motivational factors and other baseline characteristics can be expected to be similar before and after randomization.

In feasibility trials, treatment groups may include individuals who have a strong preference for that treatment over the alternative treatment and individuals who had no preference but had to decide on a method of treatment. Patients involved in a PRPT are not pressured to choose a particular type of treatment. Only those individuals with strong preferences are allocated to the treatment group preferred; patients who do not have strong preferences are asked if they would agree to be randomized. The randomized and preferences groups of the PRPT allow comparisons to be made at baseline to look for and measure differences between randomized and nonrandomized groups using each treatment in the trial with a view to understanding any between-group differences in outcome.

Advantages of PRPTs Compared With Randomized Controlled Trials

RCTs are currently viewed by the majority of medical researchers as the gold standard for

clinical trial design, and a lack of randomization is usually seen as a weakness or flaw in a study. The assumption that RCT designs are the only acceptable way to conduct clinical trials may have led to some new treatments being used without evaluation and studies to remain unpublished because randomization was deemed to be unsuitable or unethical or was refused by patients. These studies might take place using a PRPT where ethical approval and patient acceptance could be gained from the incorporation of an element of choice of treatment type in the design.

Randomization aims to avoid the limitations of a feasibility study such as the introduction of selection bias, which can affect comparability of treatment groups and different patient characteristics affecting treatment choice. However, most proponents of RCTs have wrongly assumed that randomization always produces comparable groups and have overlooked the fact that randomization itself can create between-group differences as a result of disappointment effects. The PRPT design aims to deal with the limitations of an RCT, optimizing motivational factors in those with strong preferences and equalizing motivational factors in the randomized groups within the PRPT. The effects of motivational factors on treatment outcome can be considered by comparing those who chose a treatment with those who were content to accept randomization.

Larger numbers of participants are likely to be recruited into a PRPT over an RCT, especially in certain areas of medicine such as gynecology and obstetrics, where preferences are strong. In a clinical trial comparing treatments for menorrhagia conducted by Cooper and colleagues, the majority of women recruited (97%) agreed to participate in the PRPT design compared with 70% who agreed to take part in the conventional RCT. The 40% relative increase in participants agreeing to participate in the PRPT suggests an increase in perceived acceptability of a PRPT over a RCT where patients are likely to have strong views concerning treatment.

It is more difficult to recruit patients with a preference for a conventional treatment readily available outside the trial. Therefore, the majority of participants in an RCT will be biased in favor of the new treatment and less likely to make a nonpreferred treatment work as well as a preferred treatment. In RCTs, people are likely to be more disappointed if allocated to the conventional treatment group and this problem is likely to arise whenever a new treatment is only available to patients within a clinical trial. Therefore, the overall sample studied in a PRPT or in a feasibility study is likely to be more representative of clinical reality and less biased by the effects of the experimental manipulation. The disappointed patients in an RCT who are randomized to the nonpreferred, conventional treatment, if they remain in the trial, are more likely to stop following the standard treatment recommendations and do less well, leading to artificially advantageous conclusions favoring the new treatment. The extent of the advantage overestimation will be dependent upon the proportion of disappointed patients who remain in the trial. If these disappointed patients drop out, outcomes will be artificially improved in the randomized conventional treatment group (Group 4 in figure 1). Outcomes of PRPTs are likely to be more successful than those found in a conventional RCT as the patients in a PRPT with strong views are generally more likely to make their treatment work. Torgerson and colleagues recommend as an alternative to PRPTs that preferences be measured in RCTs and subgroup analyses conducted to examine the impact of preferences. However, the RCT may lose patients with the strongest preferences at least for the standard treatment and maybe for both treatments, who then won't be available for such analyses, biasing the conclusions of the RCT. Thus, although Torgerson and colleagues' approach may enhance the value of RCTs, it does not provide a substitute for PRPTs.

Limitations

The cost difference between a clinical trial that uses an RCT design and one that uses a PRPT design is sometimes cited as a reason for opting for a conventional RCT design. More resources are required by a PRPT as twice as many groups are potentially involved in the trial compared with those included in an RCT. Patients who had a preference for the control treatment are followed up in a PRPT. These patients would probably not be recruited or followed up in an RCT. Patients with a preference for the new treatment unavailable to them outside the trial would probably be recruited into an RCT, but disappointment effects can result and distort the findings of an RCT.

The cost savings of an RCT must be weighed against the loss of internal and external validity due to having a nonrepresentative sample and outcomes which are potentially distorted by disappointment effects. Even when disappointment effects in an RCT are minimized to those of a PRPT (i.e., when both treatments being compared are available outside the trial), the PRPT still retains the advantage of recruiting a representative sample, not just those willing to be randomized, but also those with strong preferences who would decline to participate if it meant they might be randomized to a nonpreferred treatment.

Implementation

There are several steps which need to be followed by clinical trialists to ensure a PRPT design is implemented appropriately. Patients must be given detailed and accurate information about all the treatments which are available in the trial, including the possible side effects and likely effects of treatment on lifestyle and quality of life. Only when such information is provided can patients make judgments about which treatment, if any, they prefer. Patients should then be asked if they have a strong preference for one or other

treatment *before* they are asked if they are willing to have their treatment determined at random. Patients with strong preferences are then allocated to their preferred treatment group and the remaining patients are said to be in equipoise; they have been informed of the treatments but have no clear preference and can have treatment allocated at random to create two comparable groups.

If the procedure used to recruit patients in a PRPT fails to achieve equipoise in the patients to have treatment allocated at random, the randomization process cannot create two similar groups for comparison. Consider, for example, Henshaw et al's article which reported a PRPT design comparing medical versus surgical abortion. The trial was presented the trial to patients in a patient information sheet as if it were a conventional RCT. If patients refused to participate, then the clinician informed them they could, in fact, have their preferred treatment. However, it is likely that not all patients with strong preferences will decline to be randomized, particularly if they believe that their preferred treatment is only available within the trial. The randomized groups may therefore have contained patients with strong preferences, and if so, those groups will not have been comparable. Disappointment effects may have distorted the findings from the randomized groups compared with the results from randomized groups including only patients in equipoise. The impact of disappointment effects in this trial of different methods of pregnancy termination is likely to have been less than would be the case for participative treatments for long-term conditions where disappointment may impact on adherence and impair biomedical outcomes as well as quality of life and other patient-reported outcomes. Despite these concerns, the procedures used by Henshaw et al. have been followed by many subsequent trialists adopting the PRPT design to study more participative treatments.

A systematic review of 32 trials that took account of preferences was reported in the *Journal of the American Medical Association* by King and colleagues in 2005. Twenty-seven

of these trials used PRPT designs referred to as “comprehensive cohort trials,” and five were referred to as “two-stage randomized trials,” involving an initial randomization to PRPT or RCT and then subsequent randomization within the RCT or for those patients in equipoise within the PRPT. The 32 trials covering a range of clinical areas (gynecology, depression, and cancer among them) included some PRPTs that were inappropriately implemented and others where implementation was insufficiently well specified to determine appropriateness. Trialists did not usually report whether or not the treatments under investigation in the trial were available outside the trial, and it was unclear whether patients believed the treatments to be available outside the trial. If patients assumed that a new treatment under investigation was only available to them within the trial, those with a strong preference for the new treatment would have been likely to agree to take part in the trial and undergo randomization (if they were not initially asked if they had a preference) in order to have a 50% chance of obtaining the new, preferred treatment. Those with a preference for the standard control treatment may assume they could have that existing treatment outside the trial and decline to participate. This is where optimally conducted PRPTs are necessary to avoid disappointment effects and treatment-related attrition which undermine RCTs. Critiques of King et al.’s review point out that the authors overlooked the critical difference between the randomized arms of an RCT, which, when the treatments are not both available outside the trial, may be biased by disappointment effects and drop outs, and the randomised arm of a PRPT where, when properly implemented, patient equipoise is achieved and biases eliminated.

In those trials that included a description of allocation of intervention among those reviewed by King and colleagues, the majority followed Henshaw and colleagues’ example of only offering participants a choice of treatment if they refused randomization. The likely result is the inclusion of patients with preferences (who did not refuse randomization) in the randomized groups and therefore randomized groups which were not in equipoise.

The randomized groups within PRPTs should not be assumed to be the same as those in a conventional RCT. Properly conducted, the randomized groups in a PRPT will be cleared of patients with preferences, leaving only those in equipoise and removing the risk of disappointment effects that are seen in RCTs when patients have preference. Even improperly conducted PRPTs that only offer choice when patients decline randomization will have a reduced risk of disappointment effects compared with those seen in RCTs. If one wishes to examine the impact of patient preferences on the outcome of trials, one needs to compare the randomized groups of a properly conducted PRPT (where patients have no strong preferences) with randomized groups in an RCT of the same new treatment only available within the trial and which patients are keen to use. The RCT groups will include patients with preferences, and disappointment effects will be likely in the group allocated to the non-preferred standard control treatment. Two-stage randomized trials where patients are unaware of the initial stage of randomization to a PRPT or RCT design are ideal for comparing the randomized groups of a PRPT with those of an RCT but differences should only be expected when at least some patients have strong preferences for one of the treatments which is only available in the trial. If treatments are believed by patients to be available outside the trial, even the randomized groups of an RCT may be free of disappointment effects as those with preferences decline randomization and seek their preferred treatment outside the trial. Proponents of PRPTs consider King et al's conclusions that RCTs remain the gold standard and that intervention preferences appear to have limited impact on the external or internal validity of randomized trials' unjustified and misleading. The preferred method of determining the impact of preferences on outcomes of randomized trials is to compare the randomized groups of a well-conducted PRPT (cleaned of preferences) and the randomized groups of an RCT where preferences remain and can be disappointed at randomization rather than the method employed by King et al., which compared preference groups assigned to

their preferred treatment with randomized groups who had few, if any, preferences to be thwarted, from within the same PRPT.

Optimal Use

In a PRPT, participants are given a choice of treatment and only those without a strong preference (i.e., in equipoise) are asked if they will be randomized—all others being given their preferred treatment. This ensures that none of those in the randomized arms are likely to experience the disappointment effects often experienced in conventional RCTs and dropouts will be kept to a minimum. The PRPT design is particularly important in the treatment of long-term conditions, participative treatments, and treatments that have very different implications for patients (e.g., surgery vs.long-term medication). Where trial treatments are readily available outside the trial and patients know that they can have a preferred treatment if they decline to participate in a trial, the results of an RCT are likely to be similar to the results obtained from the randomized subgroups of a PRPT. However, the PRPT provides the opportunity to study the outcomes in patients who have strong preferences and are given their preferred treatment as well as studying patients in equipoise. Where a new treatment is only available within a trial and patients participate in the hope of having the new treatment, the results of an RCT are likely to be distorted by disappointment effects that can be avoided by using a properly implemented PRPT design.

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FURTHER READINGS

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