Adapting the randomized consent (Zelen) design for trials of behavioural interventions for chronic disease: feasibility study

Rona Campbell, Tim Peters[1], Clare Grant[1], Brian Quilty[2], Paul Dieppe[3]

Department of Social Medicine; [1]Academic Unit of Primary Health Care, Department of Community Based Medicine; [2]Department of Medicine (Rheumatology); [3]MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol, Bristol, UK

Objectives: **Standard randomized controlled trials of interventions for chronic conditions that involve behavioural change, or that are highly desired by participants, are difficult to undertake because of problems with recruitment and contamination. Alternatives include cluster-randomized trials or pre-randomization designs such as the Zelen design. The aim here was to develop a pre-randomization design that would overcome ethical and methodological problems associated with the conventional Zelen design, and permit the rigorous evaluation of a complex package of care, involving physical therapy and behavioural changes, for patients with painful patello-femoral osteoarthritis of the knee joint.**

Methods: **Eligible patients were first consented to a one-year observational study of their arthritis. They were subsequently randomized into intervention and control arms. Those in the intervention arm were then asked if they were willing to participate in a further study involving regular sessions with a physiotherapist. Those in the control arm were not told about this, but were followed up as agreed.**

Results: **Eighty-seven patients consented to the observational study, 43 of whom were subsequently randomized to the intervention arm. All 43 consented to the intervention, although five of these did not receive the full package of care. Assessments were carried out at five months and one year on 82 patients, and concealment was satisfactorily maintained in the majority.**

Conclusions: **We conclude that this study design could potentially offer an acceptable compromise between the need for scientific rigour and the ethical imperative of fully informed consent in trials that involve behavioural change or interventions that patients might want to obtain.**

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Introduction

Trials involving pre-randomization or randomized consent, such as the Zelen design, are controversial.[1,2] This paper uses a successful example of such a trial to suggest that there may be an important role for such designs in assessing interventions for chronic disease that have a behavioural component.

In conventional randomized controlled trials (RCTs), agreement to participate is obtained from eligible individuals, followed by random allocation to one of a number of treatment alternatives. In general, the two main ethical prerequisites for such studies are equipoise regarding the most effective treatment and fully informed consent. The second of these is especially problematic in situations where any description of the alternative treatments constitutes a partial intervention in its own right. For example, a recently reported trial of a primary care-based intervention designed to reduce repeat deliberate self-harm would have been invalidated by fully informed consent of people in the control groups.[3] This concern is a special case of the more general issue of contamination in trials. A variety of modifications to the basic RCT design have been proposed to overcome this problem, including cluster trials, deferred treatment trials and pre-diagnosis designs. Cluster trials minimize contamination post-randomization but, as in the case of the deliberate self-harm trial,[3] still leave unresolved the question of how much information about the interventions should be revealed in advance of allocation.[4] Deferred treatment designs involve patients being randomized to receive the intervention immediately, or after the main trial follow-up.[5] These designs are especially suitable in situations where patients are unlikely to be able to access the intervention outwith the trial.

Rona Campbell PhD, Department of Social Medicine, University of Bristol, Canynge Hall, Whiteladies Road, Bristol BS8 2PR, UK. **Tim J Peters PhD**, Professor, **Dr Clare Grant MD**, Academic Unit of Primary Health Care, Department of Community Based Medicine, University of Bristol, Bristol, UK. **Dr Brian Quilty MD**, Department of Medicine (Rheumatology), University of Bristol, Bristol, UK. **Paul Dieppe MD**, Professor, MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol, Bristol, UK.

Correspondence to: Rona.Campbell@bristol.ac.uk

In situations where a cluster trial is either not possible, or not desirable, a suggested solution is the randomized consent design.[1] Here consent to participate in the trial is only obtained from those allocated to a non-standard treatment arm. This design was originally proposed as a way of maximizing recruitment by only seeking consent to participate from those already randomized to the intervention arm. This, it was hoped, would maximize external validity and statistical power while maintaining an acceptable level of internal validity. Its progenitor, Marvin Zelen, hoped that such a design would encourage more physicians to participate in randomized trials because it would help to overcome the difficulties that health professionals can experience in explaining equipoise, and reduce the discomfort for both clinician and patient in acknowledging uncertainty.[1] While not necessarily undesirable, such difficulties can have an adverse effect on recruitment, both overall and in increasing selection bias.[6]

This design has not been widely used for a variety of methodological and ethical reasons.[2,6] The main methodological objection is that the differential consenting procedure results in randomization groups that are not sufficiently comparable to permit a valid intention-to-treat analysis. A second concern is that if consent is required for follow-up, which is the case for all outcomes that are not routinely recorded, then the advantages of a Zelen design may be minimal. Routine outcomes are unlikely to suffice in pragmatic trials in general, and in those testing behavioural interventions in particular. Concomitant statistical drawbacks have also been identified, including the need to have a larger number of patients randomized to achieve the same statistical power as in a conventional trial, the likelihood that the treatment difference will be underestimated to an even greater extent than is generally the case with intention-to treat analyses, and that the transfer rate of patients from the allocated treatment, which cannot be known in advance, will affect the number of patients needed to be randomized and hence the duration of the trial.[7]

The central ethical concern, though, remains that of not obtaining fully informed consent from all participants. However, although extremely important, this is not regarded as an absolute requirement by those charged with the responsibility of granting ethical approval for research on human subjects.[8,9] Cluster randomized trials involving routinely available outcomes do not necessarily obtain individual consent.[3,10]

For interventions involving behavioural change, a further alternative to a cluster randomized or pre-randomization consent design is a conventional randomized trial, but one that offers those randomized to the control (no treatment) arm the option of having the intervention after the end of the trial. Such a design, however, does not solve the problem of contamination as those in the control arm could still adopt the behavioural change before the end of the trial.

The aim of this paper, then, is to describe a trial that employed a modified Zelen design, which attempted to surmount the main ethical and methodological drawbacks of the standard randomized consent design. The main trial findings and a nested qualitative study are reported elsewhere;[11–13] the emphasis here is on the feasibility and acceptability of the approach taken to recruitment and consent.

Background to the trial

Osteoarthritis (OA) is the most common cause of chronic pain and physical disability in older people, and is a major public health problem.[14] There is, as yet, no treatment that can prevent or control the disease process; however, there are a large number of options available to reduce the symptoms and impact of the condition. These include drugs, surgery, physical therapy and a variety of behavioural interventions, such as unsupervised exercises and exhortations to lose weight.[15] Recent reviews of the literature have shown that behavioural interventions and physical therapies lack a strong evidence base, although they are popular with both doctors and patients.[16,17]

One problem that may have made it difficult to accrue robust evidence on behavioural or physical interventions for OA is the difficulty that researchers have in recruiting control groups that do not become contaminated with the intervention. There is generally no placebo available for these therapies, so in order to obtain estimates of absolute effects it is necessary to compare them with no treatment. However, patients may be less likely to agree to participate in a trial when one of the alternatives involves no treatment. In addition, those who are told that the intervention being tested is behavioural may choose to adopt the approach, regardless of their subsequent allocation, on the basis that they believe the researchers must think it is worthwhile. This may well dilute any differences between the randomized groups, especially since those in the control arm who both sought and received the intervention would constitute a highly selected and motivated subgroup. While such biases could be investigated through secondary analyses, statistical power would be low – and in any case, the problem with the primary intention-to-treat analysis would remain.

We therefore employed a modified randomized consent design as a way of overcoming these problems. The objective was to conduct a high-quality RCT to assess the effectiveness of a combined physical and behavioural intervention for patello-femoral joint OA.

Methods

Ascertainment of patients

People reporting chronic knee pain and who had radiographic evidence of patello-femoral OA (presence of osteophytes), identified as part of a large community-based cohort study carried out in 1995–1997,[18] were pre-screened for suitability by a telephone call enquiring whether they still had problems and, if so, about

any current treatment. Those still in pain and not currently being treated with physical therapy were considered potentially eligible, and were invited to attend a clinic for examination and provision of formal consent to take part in an observational study.[12]

Randomization and consent

A modification of Zelen's design was used, which is best described as a single-consent design (where consent is only sought from the intervention group) nested within an observational study for which prior consent was obtained. The trial design and consent procedure are illustrated in Figure 1. Following clinical examination, those still considered eligible for the study were asked if they would consent to inclusion in a one-year observational study of their knee OA and its relationship to quadriceps muscle strength. Patients were given a written information sheet which explained the purpose of the observational study and that their participation would involve them having measurements taken at baseline, five and 12 months. Patients were encouraged to ask if they had any questions about the research. Those who consented to the observational study were then randomized into treatment and control groups. After the initial baseline visit, the treating physiotherapist opened sequentially numbered opaque sealed envelopes containing the allocation. Those patients randomized to the treatment group were given an additional written patient information leaflet which explained the further study to test the effectiveness of physiotherapy and exercise treatment for OA, and were invited to take part. These patients were contacted at home by telephone a few days later to check if they were still willing to participate. If they agreed, they were then asked to provide a second consent relating to the intervention. No attempt was made to influence any other treatment received by either group. In particular, the control group was not informed of their allocation, nor of the existence of the further trial. To limit casual contact between treatment and control groups, patients were assessed individually at all follow-up visits. The assessor at all follow-up visits remained unaware of allocation status, with those in the treatment group asked not to reveal their allocation status. As a check of this concealment, at the end of the study, but before unblinding, the outcome assessor was asked to say which of the patients had received the active intervention.

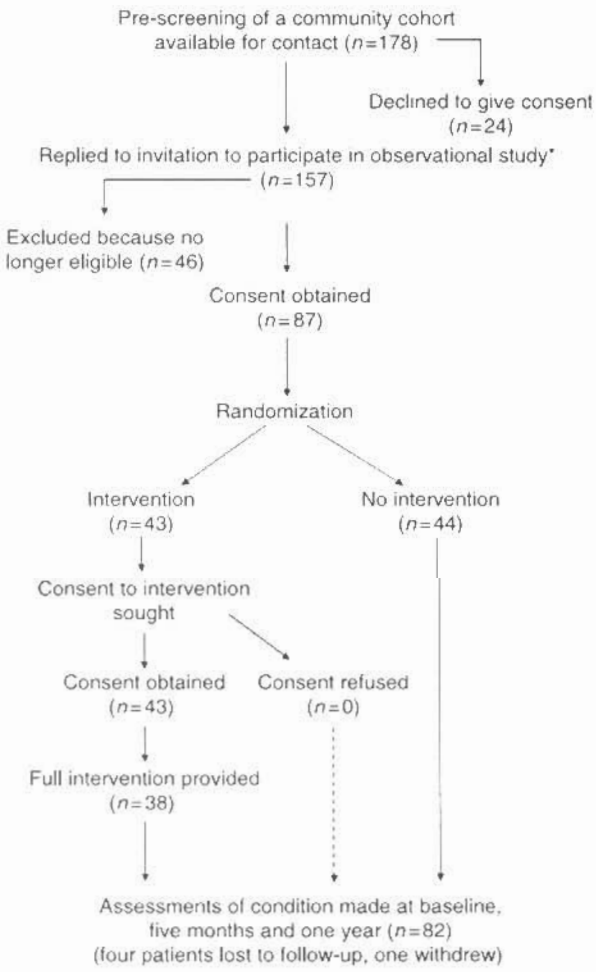

Figure 1 The procedure used for this trial: a single consent design nested within an observational study for which prior consent was obtained. *This includes three patients recruited from a rheumatology clinic

Formal ethical review

Five separate local research ethics committees gave ethical approval for the study design. Only one committee commented, noting that the design had been agreed after considerable debate.

The intervention

At the baseline examination visit (before randomization), all patients had a half-hour discussion with the physiotherapist concerning diagnosis, prognosis, weight reduction and activity. Exercise was encouraged as one of a number of general measures that help OA, but no specific exercises were advised. Patients randomized and consenting to the active treatment underwent a further assessment lasting approximately 1 h, followed by eight or nine treatment sessions over an eight-week period, lasting half an hour each and carried out in a community setting. The intervention consisted of patellar taping,[19] simple functional exercises, an isometric exercise to strengthen the quadriceps muscle and selective quadriceps exercises aimed at strengthening the muscle that stabilizes the patella. Patients in the treatment arm were given information sheets and strongly encouraged to continue with the exercises after the formal period of supervised therapy.

Outcome measures and statistical analyses

The primary outcome measures for the main RCT were overall pain in the index knee (the more painful one) as measured by a visual analogue scale (VAS), and self-reported disability as represented by the appropriate subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).[20] Assessments were made in both treatment and control groups at baseline, and five and 12 months later. The primary analysis for the trial involved intention-to-treat regression models for the clinical outcomes, comparing the groups as randomized.[12,13] In this paper the focus is on process measures indicating the feasibility of the basic design: specifically, recruitment, loss to follow-up and missing data, delivery of the intervention and success of concealment. The main trial findings are included only insofar as their plausibility provides evidence for the internal validity of the trial design.

Results

Of the 178 eligible patients identified from the community cohort, 87 (49%) were recruited to the observational study, of whom 43 were assigned to the treatment arm and 44 to the control group (Figure 1). While all patients in the intervention arm accepted the allocation, five did not subsequently receive the full intervention because they were unable to attend all of the physiotherapy sessions. One patient from the control arm and three from the intervention arm were lost to follow-up. By the end of the study, eight patients (19%) in the treatment group had revealed their allocation status during the trial. Of the remaining 79, the assessor correctly guessed the allocation of only 43 patients, close to what would be expected by chance.

The primary outcomes are shown in Table 1, with all patients followed up providing data for these analyses. From baseline to the first follow-up, there was a greater reduction in overall pain in the index knee in the intervention group compared with the control group. Comparisons for VAS pain at either follow-up time point did not show significant differences between the groups, however, and the estimated treatment effect size at five months was small (0.19 of a standard deviation). There were also no statistically significant between-group differences in WOMAC disability scores at any time.

There were no major adverse effects associated with the treatment, although seven out of the 38 patients receiving full treatment in the intervention group experienced mild and short-lived skin reactions associated with prolonged use of the zinc oxide patellar tape.

Discussion

Our objective when designing this trial was to test the effectiveness of a complex intervention for patello-femoral knee OA, including physical therapy and an attempt to change patients' behaviour (exhorting them to increase general exercise and carry out specific muscle exercises on a regular basis). Our concern was that fully informed consent in a control group would lead to their following the exercise regime given to the intervention group, and thus that a conventional randomized trial was problematic both in terms of recruitment and contamination. Therefore, a randomized consent design was employed. Since outcome measures were not available from routine sources, the standard single consent design (where consent is only obtained from the intervention group)[22] was not possible. Moreover, the double consent design (where consent is obtained from both groups between randomization and follow-up) would be unlikely to confer any advantages over a conventional trial design – indeed, this could be seen to be the least acceptable compromise between informed consent and trial validity. For this study, then, consent to follow-up was obtained from all participants prior to randomization, albeit within the context of an observational rather than an experimental study, with consent to treatment allocation only obtained from the intervention group. It was hoped that one advantage of this novel design (single consent nested within an observational study for which consent was obtained) would be to minimize the risk of post-randomization attrition, while retaining the general advantage of randomized consent designs in reducing contamination between trial arms.

Having conducted the trial, a number of crucial issues needed to be addressed. These included: internal validity, external validity, clinical importance (including the issue of power) and a general

Table 1 Comparison between main outcome measures for those in the intervention and control groups of the knee pain trial

Outcome measure	Time point (months)	Mean treatment (SD)	Mean control (SD)	Adjusted difference between means*	95% CI	P
VAS pain index knee (mm)	0	51.0 (29.3)	53.4 (25.9)			
	5	41.8 (25.2)	49.4 (26.6)	−6.5	−16.1, 2.9	0.17
	12	47.3 (24.6)	53.9 (22.7)	−5.3	−14.3, 2.7	0.25
WOMAC function (scale 0–68)	0	27.4 (12.2)	27.8 (10.1)			
	5	25.8 (12.9)	27.8 (10.5)	−0.9	−4.1, 2.5	0.61
	12	29.4 (11.2)	28.4 (10.9)	1.6	−2.2, 5.3	0.41

*Differences between means, confidence intervals and *P* values are derived from ANCOVA; SD, standard deviation; CI, confidence interval; VAS, visual analogue scale; WOMAC, Western Ontario McMaster Universities Osteoarthritis Index

interpretation and explanation of the results. Clinical importance and interpretation are covered in the main trial reports.[11–13] For the purposes of this paper, it is the validity issues that are the most pertinent.

One potential disadvantage of a phased consent procedure is that refusal could compromise external validity. In this trial, ignoring three patients recruited from clinics, of the 178 potentially suitable cases identified from a large community cohort study, 24 could not be contacted and the remaining 154 expressed some interest in participating in an observational study. After telephone contact, however, it became evident that 46 of these people were no longer suitable for inclusion. Only 24 people actually declined to participate after having been identified as suitable. Thus, assuming as a worst case scenario that all of the 24 who could not be contacted were eligible, the participation rate in this study was 64% (84/132). This is relatively high compared with many trials, and it may be that the procedure adopted (consent to an observational study) could result in higher recruitment rates than for a standard intervention trial. In terms of internal validity, loss to follow-up after randomization to the intervention was negligible. Although often considered a problem with the randomized consent design, this was not our experience. The most likely reasons for this are that all participants had already consented to follow-up as part of the observational study, and that the treatment was well regarded by those randomized to the intervention arm and did not involve a significant risk of adverse effects. Our design resulted in virtually maximum comparability of groups at baseline and follow-up (Table 1). Even if there had been greater loss to follow-up, it is unlikely that this would have been highly differential across the groups given the level of acceptability of the intervention provided here. Moreover, while formal double blinding was not possible, the results do indicate that with few exceptions the observer was effectively unaware of treatment allocation. There was no indication that anyone in the control arm became aware of the trial.

The randomized consent design was first described in 1979,[1] but has rarely been used.[6] It has been dismissed as unethical[2] as well as being justifiably criticized because of the risks of loss of patients from one group only, and difficulties in concealment and blinding.[21,22] Anecdotal evidence suggests that research ethics committees' responses to proposals involving randomized consent and cluster randomized trials vary considerably. This is frustrating for researchers, but unsurprising given the considerable ethical debate about what constitutes informed consent and the extent to which this is an absolute requirement of any research.[23–26]

To date, the randomized consent design has been employed most regularly in three main contexts – cancer, neonatology and heroin dependency.[27–29] The rationale, in most cases, has largely been that the provision of fully informed consent prior to randomization would lead to far too much unnecessary anxiety and distress, an alternative rationale being that the intervention is highly desired by potential patients. The assumption that the randomized consent design can be justified as a method of avoiding potential distress has been examined in one neonatal study; this was investigated hypothetically rather than on the basis of direct experience, and parents' opinions were evenly divided between those who thought the method acceptable or not.[27] One limitation of our study is that we did not conduct such an enquiry at the end of the trial – specifically, we have no information on the views of the participants regarding the design. If such designs are employed in the future, we would strongly recommend further research of this kind. In addition, we also recommend that the effects of offering the intervention to those in the control group be investigated; this did not occur in the present study, in part as a consequence of the negative findings in the trial.

Another recently tested alternative to the conventional Zelen design involved patients being informed that they would be randomized but that they were not going to be fully informed about the nature of the interventions until the end of the trial, unless they specifically requested this information.[30] Only three patients out of 112 made such a request and all subsequently agreed to participate. This was a trial of analgesic efficacy for chronic pain, and the impact of the attitude of the treating physician towards the expected analgesic effect. Patient participation in the trial lasted only 24 h. Thus, further research is required to see how acceptable such a design might be in other contexts.

It is important that rigorous trials of complex packages of care for chronic conditions such as OA are carried out, including those that might be desired by patients and those that involve behavioural change. In our view, it is inevitable that compromises will have to be made between fully informed consent of the control group and the likelihood of obtaining a valid result (by avoiding bias and contamination) when designing such trials. We believe that our modification of the Zelen design offers an acceptable compromise. Our alternative would have been to design a cluster randomized trial, but use of this design would not have allowed us to standardize the intervention (using one therapist), and the numbers of patients that would have been required to power the trial were not available in the cohort used for recruitment. In conclusion, we contend that in such contexts (chronic disease, behavioural interventions and relatively safe, desirable interventions) the modified randomized consent design, in which patients first consent to an observational study, strikes a reasonable balance between the potentially competing imperatives of respect for patient autonomy and scientific rigour.

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