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# Randomized cohort trial was shown to be feasible for evaluating treatments in low back pain

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## Abstract

**Objective:** To investigate the feasibility of conducting a cohort, factorial randomized controlled trial (RCT) in the treatment of patients with low back pain (LBP).

**Study Design and Setting:** Pragmatic feasibility factorial RCT nested within an observational cohort study in two general practices in York, United Kingdom.

**Results:** Eight hundred forty-five patients aged between 18 and 65 years who had consulted their general practitioner about LBP within the preceding 12 months were mailed an invitation to participate in a cohort trial, with the possibility of later joining a treatment RCT. One hundred twenty-four patients consented to participate in the cohort and treatment trial, and one consented only to the cohort only. Ultimately, 59 patients were randomized into the nested RCT. Outcomes included recruitment, acceptability, and attrition rates as measures of the feasibility of the design and Roland Morris Disability Questionnaire. No statistically significant differences in outcome between treatment groups and usual care were found.

**Conclusions:** The design was feasible for the evaluation of different back pain treatments. We found zero attrition after randomization and showed that for a remitting relapsing condition, the design allows us to recruit initially ineligible patients from the cohort. Additional statistical analysis using regression discontinuity can also be used with this design. 

*Keywords:* Cohort randomized trial; Feasibility trial; Factorial trial; Low back pain; Acupuncture; Manual therapy

## 1. Introduction

In effectiveness research, the pragmatic randomized controlled trial (RCT) aims to estimate the kind of treatment differences we would expect to see in clinical practice [1]. Thus, a pragmatic trial tries to mimic ‘‘real-life’’ clinical practice as far as possible and generally eschews design features such as the use of placebos. However, there are potential biases that might occur in pragmatic trials, such as the effect of patient preferences on treatment outcomes [2]. These problems have been recognized, and alternative trial designs such as patient preference or randomized consent designs have been proposed [2,3]. More recently, a trial design—the ‘‘cohort randomized controlled trial’’ (cRCT) approach—has been proposed that may potentially reduce some of the biases associated with unblinded trials [4]. In a cRCT, as described by Relton et al., a group of patients with the condition of interest are recruited and monitored on a regular basis. After a defined period of follow-up, an RCT is nested within the cohort study. Patients eligible for the trial are identified from the whole cohort and randomized to a trial arm. Those allocated to a treatment (as opposed to say, usual care) are then offered the treatment. All cohort patients consent to provide outcome data at enrollment into the cohort study; however, consent to receive a particular intervention is sought only from those offered the intervention.

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**What is new?**

**Key findings**

- The randomized cohort design is a novel trial method. In this feasibility study, a pilot trial of treatments for low back pain were tested using the randomized cohort trial design. The design resulted in zero attrition during the randomized follow-up; recruitment to the study design was good; patients initially ineligible due to lack of back pain could be recruited later when they relapsed; because participants were selected on a continuous variable, regression discontinuity techniques can supplement standard trial analysis.

**What this adds to what was known?**

- Few studies have used this design, and none have used it in back pain. This study shows that it is feasible to use the design in a population suffering from chronic musculoskeletal pain.

**What is the implication and what should change now?**

- When evaluating novel interventions in chronic musculoskeletal problems, trials should consider using a cohort randomized design.

This ''patient-centered'' informed consent replicates pragmatic health care. The risk of resentful demoralization in usual care patients is, in theory, reduced relative to a conventional RCT because the patients are not told in advance about treatments they then do not go on to receive. This in turn may minimize attrition, one of the major threats to the internal validity of any trial. On the other hand, the design can only be used for chronic conditions as it is not possible to assemble a cohort for incident conditions. Maintaining contact with the ineligible patients from the cohort may add information about context of the trial through a description of the outcomes of nontrial participants. Furthermore, continuing to follow-up ineligible cohort members may aid further recruitment if subsequently a change in the clinical symptoms makes some cohort members eligible. Aside from the introduction of this novel trial design by Relton, there is little evidence for the utility of this design. In this article, we report a feasibility trial using a slight variation of this design for the evaluation of multiple treatments for chronic back pain.

Low back pain (LBP) is a major health problem in the United Kingdom and worldwide, estimated to have a lifetime prevalence in western industrialized countries of 60–80% [5]. A survey carried out by the Department of Health in the United Kingdom in 1998 reported a population incidence of LBP of 40% over 12 months [6]. It is estimated to cost the National Health Service £1.1 billion a year, with chronic problems accounting for 80% of this cost [7]. The Chartered Society of Physiotherapy [8] reported that five million working days are lost each year to LBP and up to half a million people receive a long-term state incapacity benefit because of LBP.

National Institute for Clinical Effectiveness recommends the following physical treatments for LBP: exercise, manual therapy, and acupuncture [9]. Acupuncture has its history in Chinese medicine [10] and involves the insertion of fine needles into specified regions of the body [11]. Manual therapy involves a therapist manually delivering mobilization, massage, or manipulation of joints or soft tissues in the body. It is undertaken by specially trained professionals (physiotherapists, osteopaths, doctors, or chiropractors [9]).

The United Kingdom back pain exercise and manipulation factorial randomized trial found that spinal manipulation, a form of manual therapy, was more effective than group exercise for back pain but that a combination of both treatments saw the largest benefit over ''best care'' in general practice [12]. Acupuncture is increasingly used by physiotherapists and has been shown to be more effective than usual care [13]; however, there is relatively little evidence of its use in combination with manual therapy.

## 2. Design

This was a cohort, factorial, feasibility RCT. Participants were recruited into an 18-month cohort study investigating the quality of life and types of treatment accessed by individuals with LBP. Participants were contacted and recruited in 2011 with participants being allocated to treatment in the autumn of 2011 and the beginning of 2012. Follow-up was every 3 months.

In the study, there was a two-part consent process. Participants were identified from general practitioner (GP) records and approached initially via their GP about entering the cohort. A letter signed by the GP, a participant information sheet, and a consent form were sent to eligible individuals inviting them to participate in the cohort study if they were still experiencing their LBP. All consenting patients were then sent a second information pack containing a baseline questionnaire and a participant information sheet explaining that there would be a future treatment trial within the cohort study and inviting the recipient to express an interest in taking part in the treatment trial by sending a second consent form back to the researchers. A brief description of the potential treatments was included in the information pack.

Participants who consented only to the cohort study continued to receive follow-up outcome postal questionnaires but were not entered into the randomized trial. Participants from the cohort who consented to the treatment trial were assessed for eligibility after completing

the 3-month questionnaire. Eligibility criteria included having a score of ≥4 on the Roland Morris Disability Questionnaire (RMDQ). Eligible patients were randomized into one of four groups: usual care, acupuncture, manual therapy, or both acupuncture and manual therapy. Randomization ensured that the indication for treatment was balanced across groups. Participant preference was taken into consideration, in that if, for example, a participant wanted to take part but not receive acupuncture (eg, because of a needle phobia), they were not randomized into either the acupuncture or combined groups. Participants unwilling or unable to receive any of the treatments continued to be monitored in the observational cohort study and were not included in the comparisons between the randomized groups. Participants with a score <4 were not randomized but continued to be members of the cohort. The hypothesis was that the effects of resentful demoralization by the usual care group would be reduced because although they knew that there was a possibility of being offered an intervention, they never knew at what point the intervention was made available to the intervention groups, unlike in a ''normal'' randomized trial. Consequently, their responses to the outcome measures should not be influenced by the knowledge that they had not been allocated a treatment.

At 6 months, all patients were sent a follow-up questionnaire. For participants who had given consent for the cohort and RCT but had previously had an RMDQ score of <4, if their back pain had worsened such that their RMDQ score had increased to ≥4, they became eligible to enter the treatment trial and were given the option to be randomized.

### 2.1. Participants

We approached two general practices in the York area with a total registered patient population of 32,000. Individuals aged between 18 and 65 years who had consulted their GP in the preceding 12 months with LBP were identified from the GP databases. An upper age limit of 65 years was used to reduce the possibility of recruiting patients with back pain due to osteoporotic spinal fracture. Patients were excluded if they had symptoms of serious spinal or neurological pathology, had a history of spinal surgery, were pregnant or had given birth in the last 12 months, or were known to have received either of the trial treatments for their LBP in the previous 3 months.

### 2.2. Randomization

Participants eligible for the study were given an identification number. When a group of participants were found to be eligible for the treatment trial, their identification numbers were sent to D.T., who randomized the participants in a block that was equal to the size of the group. Randomization was conducted using the randomization function in SPSS such that exactly equal numbers were allocated to the arms within the block. The allocation was not stratified, and the characteristics of the individual participants were unknown to the researcher undertaking the allocation.

As this was a pragmatic trial to estimate the effectiveness of acupuncture and manual therapy, blinding of participants and professionals was not possible.

### 2.3. Interventions

All participants received usual care in addition to the trial treatments.

#### 2.3.1. Acupuncture

A group of experienced musculoskeletal physiotherapists with additional training in western acupuncture incorporating some traditional Chinese medicine principles delivered the acupuncture treatment. Participants followed a program of ten 30-minute acupuncture sessions, which took place weekly where possible.

#### 2.3.2. Manual therapy

Manual therapy was delivered by a group of experienced musculoskeletal physiotherapists who performed spinal mobilization and massage (manipulation techniques were not used as the recruited physiotherapists did not have the required additional training). Participants followed a program of ten 30-minute manual therapy treatment sessions, which took place weekly where possible.

#### 2.3.3. Combined manual therapy and acupuncture

For the combined manual therapy and acupuncture intervention group, participants received ten 45-minute weekly (where possible) treatment sessions incorporating both manual therapy and acupuncture from the same group of experienced musculoskeletal physiotherapists who delivered the individual interventions as described previously.

### 2.4. Outcome measures

The main outcome measures of this feasibility study were recruitment, acceptability, and attrition rates. The majority of attrition usually occurs at the first period of follow-up in an RCT; therefore, because of the 3-month ''run-in'' period, it was expected that attrition subsequent to randomization in this trial would be minimal. The primary clinical outcome was the RMDQ, selected because of its frequent use in research studies of LBP. The Modified Oswestry Disability Index Questionnaire was used as a secondary measure of back pain. For both scales, a higher score indicates more severe LBP. Outcomes were measured at cohort enrollment and at 3 monthly intervals thereafter for 18 months. This article only discusses clinical outcomes up to 6 months (ie, 3 months postrandomization for those entered into the RCT).

### 2.5. Sample size

No formal power calculation was conducted for this feasibility trial. It was aimed to achieve at least 16

participants in each trial arm to exceed the minimum recommended number of 12 [14].

### 2.6. Statistical analysis

Analyses were conducted using two-sided significance at the 5% level on an intention-to-treat basis, including all participants in the groups to which they were randomized. Analysis of this study was largely descriptive; however, a preliminary investigation into the effectiveness of the two interventions was conducted. This involved estimating the effect of (1) manual therapy alone vs. usual care; (2) acupuncture alone vs. usual care; (3) acupuncture and manual therapy vs. usual care; and (4) the combined intervention compared with each of the single treatments, on both the Roland Morris and Oswestry scores at 3 months postrandomization. For each comparison, we used analysis of covariance adjusting for the score reported immediately before randomization (hereafter referred to as ''screening score'') to obtain treatment estimates with 95% confidence intervals (CIs). This trial was not powered to detect a specific difference however, and so all analyses are exploratory.

Continuous data are summarized as mean and standard deviation (SD) and categorical data as frequency (percentage).

## 3. Results

### 3.1. Recruitment and attrition

In the summer of 2011, we mailed out to 845 patients from two GP practices who had visited their doctor for LBP in the preceding 12 months (Fig. 1). We received 125 consent forms back; 124 patients consented to participation in both the cohort and the treatment trials, and one individual consented only to the cohort trial. Seventy percent ($n = 88$) of respondents returned the baseline questionnaire subsequently sent to them. After 3 months, during which time one patient withdrew and one patient withdrew consent for the treatment trial, 59 (68%) cohort participants who had consented to being considered for the treatment trial were eligible for participation in treatment (ie, had

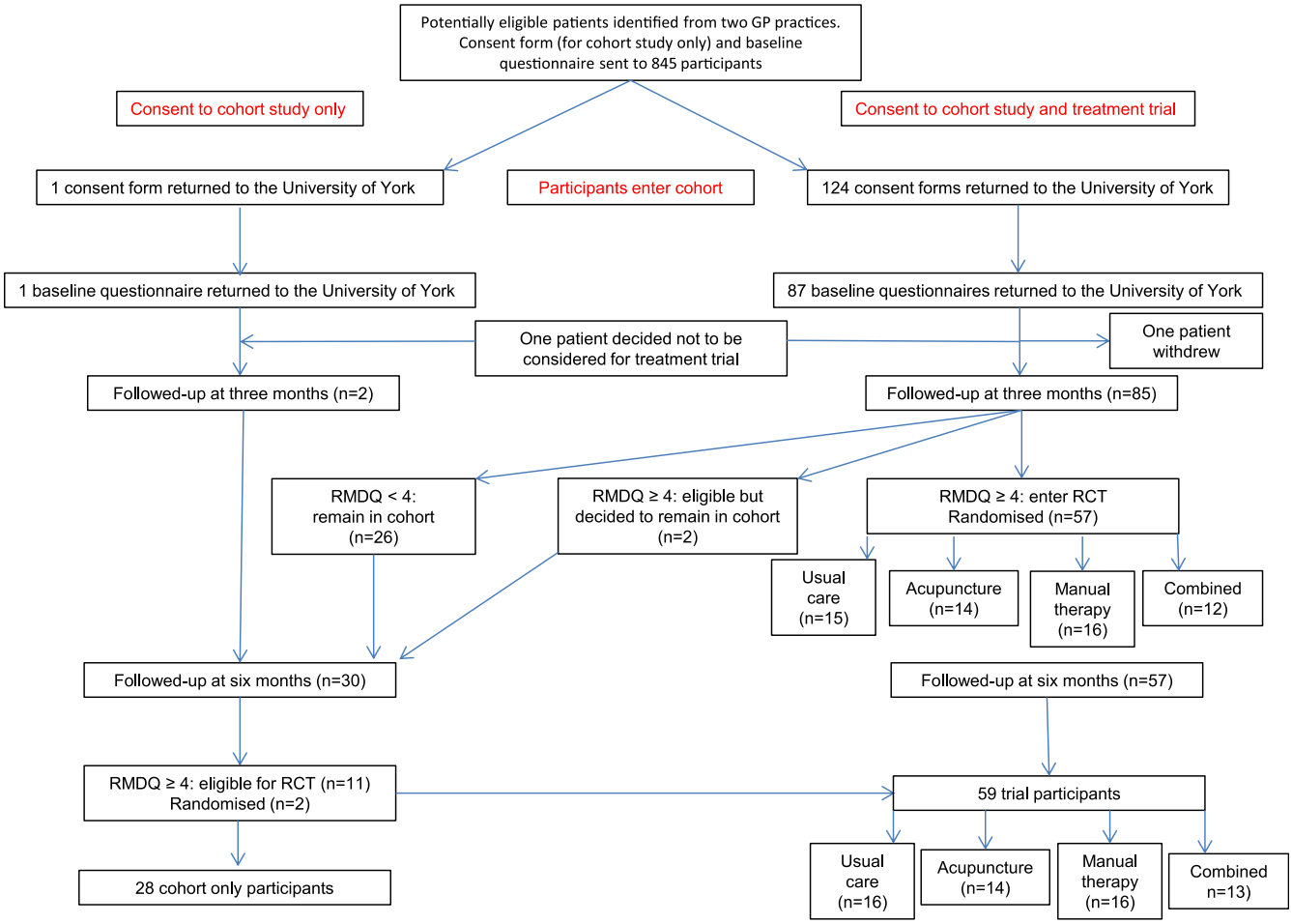


**Fig. 1.** CONSORT flow diagram. GP, General Practitioner; RCT, randomized controlled trial; RMDQ, Roland Morris Disability Questionnaire.

**Table 1.** Characteristics of cohort-only and allocated trial treatment groups

| Characteristic | Cohort only ($n$ = 28) | Usual care ($n$ = 16) | Acupuncture ($n$ = 14) | Manipulation ($n$ = 16) | Combined ($n$ = 13) |
|---|---|---|---|---|---|
| Age (yr), mean (standard deviation) | 46.3 (9.6) | 46.3 (11.3) | 45.6 (11.9) | 43.9 (13.7) | 50.1 (9.3) |
| Sex, male | 8 (29) | 5 (31) | 4 (29) | 9 (56) | 5 (38) |
| Roland Morris Questionnaire (0–24, 0 = best) | 1.8 (2.6) | 11.4 (5.3) | 8.8 (4.3) | 8.0 (4.4) | 7.0 (2.6) |
| Modified Oswestry Score (0–50, 0 = best) | 11.6 (9.7) | 29.5 (15.4) | 29.6 (12.2) | 24.0 (13.6) | 19.2 (8.0) |

an RMDQ score of ≥4). At this stage, two participants chose not to take part in the randomized trial, despite being eligible and so 57 patients were randomized. At 6 months, 11 cohort-only participants scored >4 in the RMDQ, rendering them eligible for participation in the treatment trial. Two chose to join the trial and so were randomized at this point. This was the last time point at which participants could be randomized to a trial treatment. Therefore, there were a total of 28 cohort-only participants and 59 trial participants. No participant who had been randomized withdrew up to the 3-month follow-up point postrandomization (for attrition, 95% CI: 0.0, 6.3).

### 3.2. Screening

The mean (SD) age of participants at randomization was 46 (12) years (range, 19–64 years) and 61% were female. Patients in the combined intervention group tended to be approximately 5 years older than patients in the other trial arms, and the manipulation group had almost double the proportion of women than the other three groups (Table 1).

### 3.3. Exploratory analysis—Roland Morris Disability Questionnaire

Two participants were unwilling to receive acupuncture and so were randomized only to either usual care or manual therapy. One participant was unwilling to receive manual therapy and so was randomized only to either usual care or acupuncture. These participants were excluded from any comparisons between acupuncture and manual therapy (alone or in combination). For the two patients who were randomized 6 months into the cohort study, their 6-month score has been classed as their screening score; this means however that because this article only considered data up to the 6-month time point, we do not have 3-month follow-up data for these patients. Exploratory analysis of the efficacy of the trial interventions showed that the Roland Morris Questionnaire scores improved across all groups after 3 months (Table 2). Neither acupuncture nor manual therapy produced a greater improvement in mean Roland Morris score at 3 months than usual care. For the combined group, the additional reduction in RMDQ was 2.1 points (95% CI: −2.0, 6.3) at 3 months. The greatest effect was therefore observed in the combined treatment group, although none of the differences were statistically significant.

Patients in the combined intervention group experienced on average a 1.8-point (95% CI: −1.8, 5.4; $P$ = 0.31) greater improvement in Roland Morris score than the manual therapy group and a 4.3-point (95% CI: 0.8, 7.7; $P$ = 0.02) greater improvement than the acupuncture group adjusting for screening score.

### 3.4. Exploratory analysis—Modified Oswestry Disability Index

Both the acupuncture and the combined treatment were seen to improve the modified Oswestry score more than usual care, after adjusting for screening score, and as with the Roland Morris Questionnaire, this was seen to the greatest extent in the combined group (additional improvement to usual care of 5.2 points [95% CI: −6.9, 17.3]) although statistical significance was not reached (Table 2). No

**Table 2.** Results of regression analysis of treatments for low back pain at 3 months postrandomization

| Outcome measure | Usual care (UC) | Acupuncture | Additional difference attributed to acupuncture over UC[a] (95% CI) | Manual therapy | Additional difference attributed to manual therapy over UC[a] (95% CI) | Acupuncture and manual therapy | Additional difference attributed to acupuncture and manual therapy combined over UC[a] (95% CI) |
|---|---|---|---|---|---|---|---|
| Roland Morris Questionnaire (0–24, 0 = best) | 7.4 (6.2) $n$ = 14 | 7.1 (4.6) $n$ = 13 | 0.6 (−3.8, 5.0) $P$ = 0.78 | 5.5 (6.3) $n$ = 13 | 0.4 (−4.2, 4.9) $P$ = 0.87 | 2.8 (2.7) $n$ = 12 | −2.1 (−6.3, 2.0)[b] $P$ = 0.30 |
| Modified Oswestry Score (0–50, 0 = best) | 25.4 (22.1) $n$ = 13 | 22.6 (11.7) $n$ = 13 | −2.5 (−13.9, 8.9)[b] $P$ = 0.65 | 20.6 (11.4) $n$ = 14 | 0.0 (−10.3, 10.3) $P$ = 1.0 | 10.8 (7.4) $n$ = 12 | −5.2 (−17.3, 6.9)[b] $P$ = 0.38 |

*Abbreviation*: CI, confidence interval.

[a] Estimated by analysis of covariance with adjustment for screening score.

[b] Negative differences represent a favorable outcome for the relevant intervention over usual care.

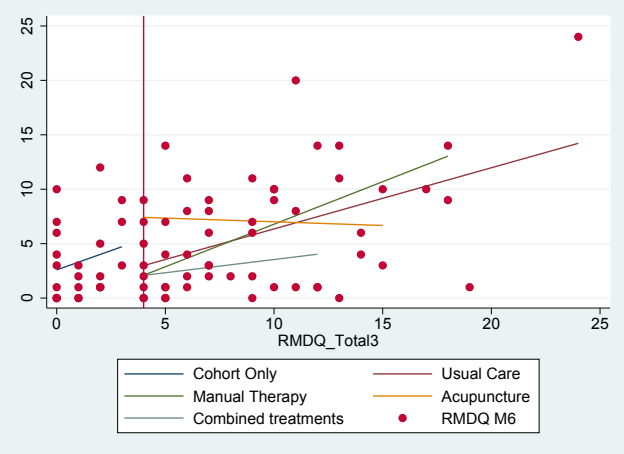


**Fig. 2.** Pre and post test correlation of RMDQ. RMDQ, Roland Morris Disability Questionnaire.

additional benefit in Oswestry score over usual care was seen in the manual therapy group.

Patients in the combined group experienced on average a 7.1-point (95% CI: 0.7, 13.6; $P = 0.03$) greater improvement in Oswestry score than the manual therapy group and a 7.4-point (95% CI: −1.7, 16.5; $P = 0.10$) greater improvement than the acupuncture group adjusting for screening score.

Fig. 2 plots the screening RMDQ scores against the scores 3 months later, with regression lines for the cohort-only group and then for each of the four trial arms.

## 4. Discussion

The aim of this study was to investigate the feasibility of conducting a cohort randomized trial in a GP setting amongst LBP sufferers. We were interested in the recruitment and attrition rates and the acceptability of acupuncture and manual therapy as a treatment for people with LBP.

We experienced a response rate to the initial mail out of 15%; 125 patients returned the consent forms, with all but one consenting to participate in both the cohort study and the nested RCT. Of the 124 patients who expressed an interest in being offered one of the trial treatments, only three people expressly stated that they would not consider one of acupuncture or manual therapy for the treatment of their LBP, indicating a high level of acceptability of these treatments. Attrition up to 6 months was extremely low in this study (1%), with only one participant withdrawing before the 3-month screening time point. One other participant contacted the researchers and stated that they did not think they would benefit from treatment because of reduced symptoms and therefore asked not to be considered for the treatment trial. No participant withdrew after randomization. This 0% attrition 3 months postrandomization compares extremely favorably with other back pain trials. For example, the three trials (UK BEAM, a cognitive behavior treatment trial for LBP, and a trial of yoga for LBP) had attrition rates of 25%, 22%, and 13%, respectively [12,15,16], which exceed our upper 95% CI limit of 6% for attrition. We are currently reporting data for up to 6 months and so cannot comment further on loss to follow rates for later on in the study.

Our study design differs slightly from that originally proposed by Relton et al. [4]. In the original Relton design, participants are not specifically told about the possibility of treatment options that could be available. The problem with this is that failure to alert the participants may mean a refusal to take up the treatment under offer, which will lead to treatment dilution. In this study, we flagged up the possibility of future treatments to avoid this problem. This study identified two extra benefits of using a randomized cohort design that was not described in the original article by Relton et al. First, using the design for a chronic remitting/relapsing condition like back pain, is that some participants, who initially were not eligible because of low symptom scores, became eligible at a later date and could be randomized. In a ‘‘normal’’ randomized trial design, these patients would have been lost from being included in the randomization. Second, by including the cohort of low symptom patients, we could, if the trial had been large enough, have supplemented the randomized analysis by including the cohort in a regression discontinuity analysis.

The limitations of this study mainly stem from the limited sample size; however, as a feasibility trial, the study was not powered to detect a difference between the trial groups in terms of Roland Morris score and so results can only be seen as exploratory. Furthermore, we excluded patients over the age of 65 years. Future trials of back pain should include older patients to enhance their external validity.

Although we have shown that the trial design is feasible, if it were scaled up, there would be additional work and cost for the researchers to follow-up the nonrandomized cohort. It is possible that this is not a cost-effective use of research resources. The nonrandomized cohort can improve recruitment in this condition as some patients may become eligible who previously were not. In a larger study, the trial-based analysis can be supplemented with a regression discontinuity analysis, which would improve study inference. However, arguably, the resources spent to obtain these benefits may be better used to increase the overall sample size of the randomizable participants. Consequently, it might be more cost effective to modify the design by not following up the ineligible participants.

## 5. Conclusion

We would recommend that this research design is used further in larger treatment trials of interventions for musculoskeletal conditions.

## References


[1] Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. J Clin Epidemiol 2009;62:499−505.

[2] Preference Collaborative Review Group. Patients' preferences within randomised trials: systematic review and patient level meta-analysis. BMJ 2008;337:a1864.

[3] Zelen M. A new design for randomized clinical trials. N Eng J Med 1979;300:1242−5.

[4] Relton C, Torgerson D, O'Cathain A, Nicholl J. Rethinking pragmatic randomised controlled trials: introducing the "cohort multiple randomised controlled trial" design. BMJ 2010;340:c1066.

[5] Maniadakis N, Gray A. The economic burden of back pain in the UK. Pain 2000;84(1):95−103.

[6] DoH. The prevalence of back pain in Great Britain in 1998. London: Government Statistical Service Bulletin; 1998:18.

[7] Critchley J, Ratcliffe J, Noonan S, Jones RH, Hurley MV. Effectiveness and cost-effectiveness of three types of physiotherapy used to reduce chronic low back pain disability: a pragmatic randomized trial with economic evaluation. Spine 2007;32(14):1474−81.

[8] Woby SR, Urmston M, Watson PJ. Self-efficacy mediates the relation between pain-related fear and outcome in chronic low back pain patients. Eur J Pain 2007;11(7):711−8.

[9] NICE. Early management of persistent non-specific low back pain. NICE Clin Guideline 2009;88.

[10] WHO. Traditional medicine and modern health care. Progress report by the Director-General. Geneva: World Health Organisation; 1991.

[11] Longbottom J. The use of acupuncture with in vitro fertilisation: is there a point? J Assoc Chartered Physiother Women Health 2008;(103):29−38.

[12] UKBEAM. United Kingdom back pain exercise and manipulation (UK BEAM) randomised trial: effectiveness of physical treatments for back pain in primary care. BMJ 2004;329:1377.

[13] Witt CM, Jena S, Selim D, Brinkhaus B, Reinhold T, Wruck K, et al. Pragmatic randomized trial evaluating the clinical and economic effectiveness of acupuncture for chronic low back pain. Am J Epidemiol 2006;164:487−96.

[14] Julious SA. Sample size of 12 per group rule of thumb for a pilot study. Pharm Stat 2005;4(4):287−91.

[15] Lamb SE, Hansen Z, Lall R, Castelnuovo E, Withers EJ, Nichols V, et al. Group cognitive behavioural treatment for low-back pain in primary care: a randomised controlled trial and cost-effectiveness analysis. Lancet 2010;375:916−23.

[16] Tilbrook HE, Cox H, Hewitt CE, Kang'ombe AR, Chuang LH, Jayakody S, et al. Yoga for chronic low back pain: a randomized trial. Ann Intern Med 2011;155:569−78.