Physiotherapy Rehabilitation for Osteoporotic Vertebral Fracture - A randomised controlled trial and economic evaluation (PROVE trial).

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ABSTRACT

Purpose: To evaluate the clinical and cost-effectiveness of different physiotherapy approaches for people with osteoporotic vertebral fracture(s) (OVF).

Methods: Prospective, multi-centre, adaptive, three arm randomised controlled trial.

615 adults with back pain, osteoporosis and at least 1 OVF participated. Interventions: 7 individual physiotherapy sessions over 12 weeks focused on either manual therapy or home exercise compared to a single session of physiotherapy education (SSPT). The co-primary outcomes were quality of life and back muscle endurance measured by the QUALEFFO-41 and Timed Loaded Standing (TLS) test at 12 months.

Results: At 12 months there were no statistically significant differences between groups. Mean QUALEFFO-41: -1.3 (exercise), -0.15 (manual) and -1.2 (SSPT), a mean difference of -0.2 (95% CI, -3.2 to 1.6) for exercise and 1.3 (95% CI, -1.8 to 2.9) for manual therapy. Mean TLS: 9.8s (exercise), 13.6s (manual) and 4.2s (SSPT), a mean increase of 5.8s (95% CI,-4.8 to 20.5) for exercise and 9.7s (95% CI, 0.1 to 24.9) for manual therapy.

Exercise provided more quality adjusted life years than SSPT but was more expensive. At 4 months significant changes above SSPT occurred in endurance and balance in manual therapy, and in endurance for those ≤70 years, in balance, mobility and walking in exercise.

Conclusions: Adherence was problematic. Benefits at 4 months did not persist and at 12 months we found no significant differences between treatments. There is inadequate evidence a short physiotherapy intervention of either manual therapy or home exercise provides long-term benefits, but arguably short-term benefits are valuable.

Trial registration ISRCTN 49117867

Mini Abstract

The trial compared three physiotherapy approaches: manual or exercise therapy compared to a single session of physiotherapy education (SSPT) for people with osteoporotic vertebral fracture(s) . At one year there were no statistically significant differences between the groups meaning there is inadequate evidence to support manual or exercise therapy.

Keywords: Osteoporosis, spinal fracture, exercise therapy, manual therapy, physical therapy, rehabilitation.

Introduction

Osteoporosis is a major public health problem that affects an estimated 3.2 million people in the United Kingdom (UK).[1] It's clinical importance lies in its association with bone fractures and their complications.[2] Vertebral fractures are the most common osteoporotic fracture and are thought to affect at least 20% of the older population in the UK; thus around 1 in 5 people aged 50 years or more will have one or more osteoporotic vertebral fractures (OVF), with the incidence and prevalence increasing rapidly with age.[2, 3]

OVFs result in increased mortality and significant morbidity, even if initially clinically asymptomatic.[3-5] They are associated with back pain, fatigue, impaired mobility, depression, restricted activity and social participation and marked reductions in quality of life (QoL) that can persist for at least 18 months after-fracture. [4-6] Vertebral fractures cause spinal deformity and alter spinal biomechanics, increasing the risk of subsequent vertebral fractures, hyperkyphosis, falls, non-vertebral fractures and restrictive lung disease.[4,5,7] Osteoporosis and fragility fractures also present a substantial economic burden; with the cost of care in the UK estimated to rise from £4.4 billion pounds in 2010 to approximately £5.5 billion pounds per year by 2025.[1]

Physiotherapy is frequently recommended for patients with symptomatic OVFs and can include a variety of exercise (strength, balance, postural exercises etc) and 'hands-on' manual therapies such as joint mobilisations and massage.[1,7,9-11] The most recent Cochrane review of exercise trials for people with vertebral fracture concluded that the evidence for the effects of exercise on performance of mobility outcomes was promising as were the effect on falls, pain and balance, but that results were variable [9]. Previous trials using manual therapy suggest that manual techniques such as mobilisations and postural taping provide increased proprioceptive feedback about postural alignment and improve thoracic extension, reduce pain and facilitate postural muscle activity and balance [9-10]. However, in these RCTs sample sizes are small, and no long term outcomes were published, so the sustainability of the effects is unknown. In conjunction physiotherapists often provide substantial education e.g.; about osteoporosis, fall prevention strategies etc.[12]

Overall, evidence of the effectiveness of exercise or manual therapy based treatment approaches is lacking. The aim of this trial was to assess the clinical and cost-effectiveness of three different physiotherapy approaches: manual therapy, exercise therapy or a single session of individually tailored education from an experienced physiotherapist.

Methods

This was a multicentre, prospective, three arm randomised controlled trial (RCT) with an adaptive design and blinded outcome assessment. It was a pragmatic trial, designed to measure the effectiveness of physiotherapy interventions in standard conditions. It took place in 21 National Health Service hospital outpatient physiotherapy centres across England. The trial was approved by the UK South Central Research Ethics Committee (REC: 12/SC/0411) and site-specific approvals were obtained. It was performed according to the published protocol, with no changes after the trial began.[13] The study and intervention protocols were designed in accordance with the CONSORT and TIDieR guidelines .

Participants

Potential participants were approached at osteoporosis clinic visits or by mail, using electronic medical records from relevant radiology or primary care clinics to identify those with OVF. They were given an invitation letter and information pack and those interested were offered an appointment with the research team to provide further information, answer questions to confirm eligibility, and if appropriate, to enrol the participant into the trial. Relevant medical and radiology records were screened, but no new radiology was undertaken at trial entry. Men and women aged 18 or over were eligible if they had a diagnosis of osteoporosis confirmed by radiograph or dual energy X-ray absorptiometry (DEXA) scan (T score -2.5 SD below young adult mean at the lowest lumbar level), at least one previous OVF (confirmed on existing radiography, magnetic resonance imaging or DEXA scan) and back pain. They also had to be able to walk at least 10 metres, be able to exercise and participate in physiotherapy safely and, if female, to be post-menopausal. There were no eligibility restrictions on the number of previous, or time since vertebral fracture, nor the location, nor severity of vertebral fracture(s). People with severe unstable cardiovascular or pulmonary disease, significant psychiatric or neurological conditions, bone loss secondary to other disease or medication, those who had undergone vertebroplasty, facet joint injection or physiotherapy in the previous 12 weeks were ineligible.

Randomisation and masking

Research clinicians confirmed participant eligibility, obtained written consent and conducted baseline assessment prior to enrolment and randomisation. The central telephone service at Warwick Clinical Trials Unit enrolled then randomised participants, allocating between a physiotherapy program of exercise therapy, manual therapy and a single session of physiotherapy (SSPT) education using a computer generated variable block randomisation schedule stratified by centre to control for confounding factors at local recruitment sites designed by the trial statistician. Research staff did not deliver treatments, and all staff conducting assessments and managing data were blinded to allocation group at all points. It was not possible to mask participants or physiotherapists providing interventions, but participants were asked not to disclose their allocation to assessors.

Outcome Assessments

Clinical outcome assessment occurred at baseline, 4 and 12 months. The timing of the primary endpoint was 12 months. The co-primary outcomes had equal weighting in the analysis plan. The co-primary outcomes were: 1) QUALEFFO-41 : a disease specific health related QoL self-report questionnaire with 5 domains (pain, physical function, social function, general health perception, mental function), total score range 0 – 100, lower scores indicate higher QoL,[14] and 2) the Timed Loaded Standing test (TLS) which records the time (in seconds) a person can stand with arms extended, shoulders flexed to 90^0 holding a 1kg weight.[15] The holding time and test end relate to back muscle endurance.[15,16] Secondary outcomes included thoracic kyphosis angle measured with a flexicurve ruler,[17] standing balance evaluated using the Functional Reach test (FR), physical function and walking capacity assessed by the Short Physical Performance Battery (SPPB), a 6-minute walk test (6MW) and Physical Activity Scale for the Elderly (PASE), and falls incidence recorded with a monthly event calendar.[18-21] Participants completed the EQ5D-5L at baseline, 4 months, 6 months and 12 months and logged healthcare use in a standardised trial diary at 4 and 12 months. Attendance and adverse events were recorded on standardised trial forms.

Interventions

Participants in manual therapy and exercise therapy were offered a one-hour assessment plus 6 individual outpatient physiotherapy sessions spread over 12 weeks with a specialist musculoskeletal physiotherapist with at least 4 years' post-graduate musculoskeletal experience. Interventions were individually tailored for each participant. Participants allocated SSPT were offered a single one-hour assessment, education and advice session with a physiotherapist. See online Appendix 1 and published protocol for further detail. [13]

Manual Therapy

Manual therapy included low velocity central posterior-anterior spinal mobilisations through the thoracic and/or lumbar spine, with vertebral level, grade (from grade 2 to 4) and number of repetitions selected individually. It also included soft tissue mobilisation, postural education including taping, and a home programme of passive stretches that promoted thoracic extension for up to 15 minutes daily.[13]

Exercise Therapy

Exercise therapy consisted of a multi-component, progressed programme of balance, strength training concentrating on back extensor and postural muscles and functional weight-bearing exercise (walking, step-ups etc).[13] Based on assessment the physiotherapist selected exercises which were sufficiently challenging and could be performed effectively, safely and comfortably from standardised, graded sets, Strength training intensity was set and monitored using the 0-10 Rating-of Perceived Exertion (RPE) scale at a participant-perceived moderate to somewhat hard level of effort(RPE level 3, 4) .[22] Balance exercises were progressed in a standard way e.g.; upper limb support to no upper limb support, eyes open to eyes closed etc. A pedometer was used to assess walking capacity, structure and progress the walking programme [3, 22] Participants were asked to continue the exercise programme at home between clinic sessions aiming to include short sessions of exercise within daily life, aiming to achieve 45 minutes per day, 3 to 5 times a week depending on ability. Strategies were employed promote adherence.[13]

Single Session of Physiotherapy (SSPT)

This consisted of general education about osteoporosis, vertebral fractures and strategies to reduce falls. It covered lifestyle choices to promote bone health including general information about diet, regular weight-bearing exercise and physical activity. Information was consistent with osteoporosis clinical guidelines and information from the Royal Osteoporosis Society (ROS, UK).[2,11,23] The participants in the manual and exercise groups received general advice only.

Physiotherapists received 4 hours of training covering theoretical and practical application of the interventions. Therapists detailed the content of all treatment sessions in a treatment log and their usual clinical records. The research team reviewed treatment logs and visited each site to conduct fidelity checks, monitoring implementation against study protocols using a proforma and ensuring each therapist received a minimum of one quality control visit per treatment type that they gave. Further visits occurred based on the outcome of the initial visit.

Sample size

No formally established minimal clinically important difference (MCID) exists for QUALEFFO-41 or TLS tests. The sample size was calculated to detect a standardised effect of 0.4 in the QUALEFFO-41; this is a modest effect size which is consistent with other modest but worthwhile treatment effects for back pain; at 80% power with an alpha of 0.05, which would require 180 to 200 participants in each group. We calculated 540-600 participants were required, allowing for 10% drop-out.

Statistical Analysis

This was an adaptive trial, in which either active intervention arm could be dropped or the trial halted at an interim analysis. The interim analysis was guided by pre-specified rules using the estimated mean change in total QUALEFFO-41 from baseline to 4 months using data from 75 participants per arm. If change from baseline in an intervention arm was no more than 0.5 points greater than SSPT, this arm would be dropped. Under this rule both arms might be dropped, and the trial terminated. A change in one arm, more than 2 points higher than the other, would result in dropping the worst performing arm. Considering this, the specified sample size gave 94% power if the better of the two intervention arms had a true standardised effect of 0.4. After accrual and follow-up of the first 75 participants, the rules were met for continuing as a three-arm trial.

There was a pre-specified statistical analysis plan. Intention to treat analyses were performed and participants were analysed in accordance with the group to which they were randomised. Baseline characteristics for participants in each arm were summarised by proportions for each level binary or categorical variables and means and standard deviations for continuous variables. We pre-specified that we would not impute missing data if the proportion of participants with missing data was less than 10% within each arm. The analyses of primary and secondary outcomes were adjusted for centre and baseline value of the outcome being considered. The analyses of primary outcomes were additionally adjusted to account for the adaptive design of the study and for the multiple comparisons arising from the two pairwise comparisons with SSPT using a closed testing procedure. We used an inverse normal combination function to combine individual and Dunnett-corrected p-values obtained from treatment comparison adjusting for centre and baseline from the datasets from the two stages. No adjustment for multiplicity was made in analysing secondary endpoints. For the primary outcomes, unbiased estimates and confidence intervals correcting for the adaptive design and multiple testing were also obtained.[24,] Results are presented as treatment effects with 95% confidence intervals and P values, statistical significance was defined as p=0.05 (two sided 5% significance level).

Pre-planned subgroup analyses investigated the interaction between age (≤70 versus >70 years), sex, baseline fracture status (≤2 versus >2) and treatment allocation on primary outcomes adjusted for centre and baseline value. A pre-specified Complier-Average Causal Effect (CACE) analysis using twostage least squares estimation was completed to determine if attendance affected primary outcomes using the number of sessions attended as an endogenous variable and adjusting for baseline and recruitment centre as exogenous variables. All analyses used R version 3.4.1 (www.R-project.org) except the CACE analysis, which used STATASE 15.0 (www.stata.com).

The cost-effectiveness analysis used EQ5D-5L and healthcare diary data collected from participants. The perspective was that of the NHS and personal social services (price year 2015/16) and the outcome was incremental cost per quality adjusted life year (QALY). The time horizon of the analysis was one year and costs and QALYs were not discounted. Missing resource use and EQ5D data were dealt with using multiple imputation where data were missing at random using predictive mean matching with five nearest neighbours. The difference in costs and QALYs was estimated with regression analysis, using a system of seemingly unrelated regressions. The probability of each intervention being the most cost-effective was estimated at a threshold of £20,000 per QALY gained.[25] Further details on the cost-effectiveness analysis are available in the online appendix, reported using the CHEERS checklist.

Adverse events

These were reported to the trial team and investigated further. They were classified through discussions with the local Principal Investigators, the Trial lead and one of the co-applicants Dr Muhammad K Javaid, a Consultant in Metabolic Bone Medicine and reviewed by the trial Data Monitoring and Efficacy Committee (DMEC).

Patient and Public Involvement

Throughout we were supported by the Royal Osteoporosis Society a UK charity, and a representative from this organisation was a co-applicant. Members of our local osteoporosis group and former patients with osteoporosis were also consulted when developing and refining trial interventions and materials. In a pilot phase at trial outset, a nested qualitative study explored the acceptability of the trial to participants. Another patient representative was a voting member of the trial steering committee and provided guidance.

Results

From September 2013 to September 2016, 1213 potentially eligible people were identified of which 615 were enrolled. In total, 63/ 615 (10%) participants withdrew and a further 17/615 (3%) were non-contactable at 4 months, rising to 23/615 (4%) at 12 months (Figure 1). The most common reason for withdrawal was death or serious other illness: exercise (n=9), manual therapy (n=11), SSPT (2). Dissatisfaction with allocated arm was higher in SSPT (n=7) than in manual (n=1) or exercise therapy (n=0). Final data was collected in September 2017.

Participants were aged from 42 to 97 years, mean age 72 (SD 9.1) years; 531/ 613 (86%) were women, 82/613 (13%) were men. The mean lumbar spine DEXA T-score was -2.7 (SD 1.3), the average number of OVFs was 2.5 (SD 1.9), most participants were hyperkyphotic and had substantially limited mobility and endurance (Table 1). The groups were well-matched at baseline. Loss to follow up was highest in the exercise arm but less than 10% in all arms. Primary data at 12 months was obtained for 529/615 (86%) participants for QUALEFFO-41 and 458/615 (75%) for TLS. Those without QUALEFFO-41 had slightly higher pain, those without TLS were more likely to have back pain currently, worse balance and kyphosis.

Intervention compliance

One participant withdrew on randomisation to SSPT, the remaining 195/196 (99%) attended. Exercise participants attended a mean 4.3 (SD 2.7) sessions; 143/216 (66%) partially complied (minimum 4 sessions) and 82/216 (38%) fully complied (7 sessions). Manual therapy participants attended a mean 5.03 (SD 2.6) sessions; 155/203 (76%) partially complied and 99/203 (49%) fully complied. Fidelity checks showed no evidence of contamination (that participants crossed arms) and that intervention content was well delivered. Common barriers to attendance were: other health problems, caring commitments and transport difficulties. Healthcare diaries showed that 50/196 (25%) SSPT participants sourced some type of additional physiotherapy (NHS or private) outside of the trial.

Adverse Effects

A total of 85 adverse events were reported but there were no serious adverse events associated with the trial, according to the pre-specified criteria. In exercise 24/216 (11%) participants reported 26 events including 5 falls and 6 fragility fractures; in manual therapy 34/203 (17%) participants reported 37 events with 6 falls and 9 fragility fractures, in SSPT 22/196 (11%) reported 22 events including 4 falls and 8 fragility fractures. Other events included: cardiovascular problems (stroke, tachycardia etc.), respiratory and urinary tract infections, minor musculoskeletal pain (shoulder, back) and other diverse conditions.

Clinical Outcomes

At 12 months there were no important differences between exercise and SSPT, nor manual therapy and SPPT (Table 2). There were no statistically significant interaction effects for pre-specified sub-group analyses, and there were no clinically or statistically significant compliance effects. Within groups total QUALEFFO-41 scores improved relative to baseline and TLS endurance increased by a mean 9.8s, or 20% (exercise), a mean 13.6s, or 28% (manual therapy) and 4.2s or 8% (SSPT). Whilst these changes were clinically significant, there were no statistically significant findings between the groups. Improvements in thoracic kyphosis were largest in the manual and exercise therapy groups over 12-months; (Table 2). Mean kyphosis reduction at 12 months was: -6.9° (exercise), -4.6° (manual therapy) and -2.7° (SSPT), changes that are recognised as clinically significant, but there were no statistically significant differences between the groups.

Although there was no statistically or clinically significant difference in outcomes at 12 months, there was some difference in the early pattern of response, measured at 4 months, with clinically and statistically significant improvements in the primary outcome of TLS endurance in manual therapy compared to SSPT and in those 70 years or younger in exercise therapy. The CACE analysis suggested improvements due to manual therapy increased with the number of sessions attended. In manual therapy compared to SSPT, TLS increased by a mean of 1.95s (95% CI 0.45 to 3.44), p=0.01 for each session attended. In home-exercise: TLS increased by a mean of 1.52 (95% CI -0.23 to 3.27), p=0.09 for each session attended. At this point there were also significant improvements in balance (FR) in both exercise and manual therapy above SSPT and significant improvements in functional mobility (SPPB and 6MW) above SSPT in exercise therapy (Table 2).

Cost-effectiveness

Exercise therapy was more effective (0.002 QALYs, 95%CI -0.020 to 0.025) but more costly than SSPT (£206, 95%CI -£228 to £641) whereas manual therapy was less effective (-0.014, 95% CI -0.036 to 0.009) and more costly than SSPT (£244, 95% CI -£195 to £683) [Table 4 and Table A.3 Online appendix]. Using a threshold of £20,000 per QALY gained, the most cost-effective option was SSPT with a probability of 69% (Table 4). Sub-group analyses indicated exercise therapy to be cost-effective for those aged 70 years or younger (£12,310 per QALY gained) but not for those over

70(52% probability). Full data on resource use, costs, EQ5D utility and cost effectiveness analysis will be published in the National Institute for Health Research health and technology assessment journals library.

Discussion

Overall, at 12 months this trial found no statistically significant differences between the three treatments and SSPT to be the most cost-effective option. All of the treatments demonstrated some degree of benefit that would be consistent with clinically important changes, but overall there was no significant difference between them.

The reduction in thoracic kyphosis in the exercise and manual therapy arms at 12 months was of a level judged clinically important in other trials. [10, 26] Thoracic kyphosis usually progresses with age and hyperkyphosis is associated with excess morbidity and mortality, so even small reductions are valuable if sustained. [8, 10, 26, 27.] Significant differences in back muscle endurance as measured by timed loaded stand were seen early after treatment but by 12 months there was no significant difference between the groups, although modest increases persisted. Back muscle fatigue and difficulty carrying out tasks in standing due to fatigue are key problems for people with OVF and chronic back pain that affect QoL.[15, 28] Back muscle weakness is also correlated negatively with kyphosis angle, associated with hyperkyphosis and an increased risk of fractures.[29-31] Most participants had poor endurance on trial entry, [15, 16] and deterioration or no improvement would be expected in this population over 12 months.[29]

The subgroup analysis highlighted improvements in endurance were experienced primarily by those 70 years or younger. Aging is associated with increased osteoporosis severity, number of comorbidities and frailty, as well as neuro-muscular changes such as sarcopenia. These factors may compound problems due to spinal pathology for older people with osteoporosis. [28] Younger participants may have had more capacity to improve and/or found home exercise and treatment attendance easier.

At 4 months balance improved significantly in both intervention arms above SSPT. A 1cm increase in FR in older adults is thought clinically relevant; [32] mean changes greater than 2cm occurred in both arms, the larger in exercise therapy potentially due to combined balance and strength training. In addition, significant, clinically relevant gains in functional mobility and walking capacity were seen in exercise therapy.[33] By 12-months, improvements in balance and mobility in intervention groups reduced in size, gains were seen in SSPT and differences were no longer significant.

Comparison with other studies

Over the trial there were no significant differences in QoL between groups as measured by total QUALEFFO-41 or EQ5D-5L. However, the improvement we saw within exercise therapy was of similar magnitude to significant findings in a trial without an active comparator.[12] Evstigneeva et al. (2016) reported larger benefits immediately after a 12-month (104 session) intervention, but here QoL deteriorated in the no-intervention control, emphasising effects and no longer follow-up occurs.[34] Five other RCTs report no significant change in total QUALEFFO-41 between groups after treatment, although one shows significant change in subscales and one in an accompanying generic QoL measure. [10, 35-38] Papaioannou et al. (2003) studying a frail cohort similar in age and disease severity to ours, found QoL improved after a 7 session home-based physiotherapy and exercise programme and a further 2 RCTs of exercise interventions in women with and without OVFs demonstrate improvements in QoL post-treatment. [39-41] These studies use other osteoporosis-specific QoL instruments. Although QUALEFFO-41 is the most common measure, whether it is the best instrument for evaluating change due to rehabilitation is unclear.[42]

Increased back strength or endurance immediately after physiotherapy has been observed in other RCTs in this population.[38, 43, 44] Improved balance immediately after treatment is also reported. [12, 34] Bergland et al. (2011) found improvements in FR of a comparable magnitude after a 12 week (24 session) exercise class intervention.[12] Improvements have been associated with reduced fear of falling,[45] but as in our trial not with significant reductions in falls at 1 year. [36, 45] The two other studies that conduct longer follow-up found, like us, when supervised intervention ceased differences between groups diminished and at 12 months changes were not significant.[12, 43]

Consistent with our trial, previous RCTs of exercise for people with OVFs have demonstrated significant improvements in functional mobility post-treatment. [12, 34] In contrast, Bennell et al. (2010) and Papaioannou et al. (2003) found no significant improvement.[38, 39] Here, whether exercise is sufficient is uncertain. Bennell et al. (2010) report good adherence but include few functional exercises, for Papaioannou et al.(2003) adherence is problematic, at 6 months only 62% (23/37) women comply exercising 3 times per week for 80% (21) of the 26 week intervention, decreasing to 46% (17/37) at 12 months.[39] In our trial mobility gains reduced and were no longer significant at 12 months. Unlike us, Bergland et al. (2011) found gains persisted at 12 months.[12] Here, exercise dose appears higher, 75% (34/45 women) attended at least 79% (19) of 24 classes, and the group format may have provided additional benefits.[12]

Strengths and limitations of this study

This trial is the largest RCT to assess physiotherapy for people with OVFs to date and the first to provide information about cost effectiveness. Most participants had severe osteoporosis; characterised by multiple OVFs, hyperkyphosis, back pain, poor back muscle endurance and limited exercise capacity. The trial was well conducted and pragmatic, designed to test interventions deliverable in routine practice to enhance the applicability of findings. Contrary to most previous studies it evaluated longer term effects of interventions.

However, our intervention was potentially too low in intensity or duration to sustain improvements. Determining the intervention dose was challenging, models of treatment delivery in RCTs in similar populations vary widely e.g.; from an individual sessions plus daily home-based self-directed exercise, to 104 class sessions over 12 months.[34, 40] Although 7 sessions across 12 weeks seems limited when compared to prolonged exercise class interventions, previous trials with individual sessions and home programmes reported benefits and individual sessions are required for manual treatments. [10, 12, 34-41,43, 44] Our interventions resembled these trials and tested a common model of service delivery i.e.: outpatient physiotherapy rehabilitation plus a self-directed home program that was feasible to deliver within a publicly funded healthcare system.

An issue specific to the cost effectiveness analysis was the missing EQ5D and patient diary data. Complete EQ5D-5L and cost data was available for only 242/ 613 (40%) of participants. However, the sensitivity analysis explored the impact of different imputation models and SSPT remained the most cost-effective intervention at 12 months.

Our comparator was education by a physiotherapist and 25 % (50/196) participants in SSPT sourced additional physiotherapy of some kind outside of the trial. Our results show that unlike trials with no treatment comparators that report deterioration, small gains were seen in SSPT in most outcomes, against the expected disease course and suggestive of static success. These gains may represent a placebo response, educational benefits, or the effect of physiotherapy treatment sourced outside of the trial but reduced between group difference.   Furthermore, most participants did not receive the planned intervention intensity, potentially resulting in smaller treatment effects in both intervention groups. This was highlighted by the CACE analysis which suggested those who attended more sessions experienced greater benefits. Other studies of both class and individual interventions have also reported problems with compliance.[10, 38, 43, 44, 46] Direct comparisons are complex as compliance is defined and measured in varied ways across studies. For example; Bautmans et al. (2010) report 15/29 (52%) participants comply, attending 50% (9/18) physiotherapy sessions over 12 weeks, Gold et al. (2004) noted 94 participants attended an average 58% (70/120) exercise classes, or see Papaioannou et al.(2003) (discussed above).[10, 38, 43] Multiple factors affect treatment adherence in older people with chronic diseases such as osteoporosis; problems with transport, caring commitments and ill-health were common barriers to attendance reported by participants in our trial, but other personal and programme characteristics might be influential.[47] Overall, these factors potentially resulted in smaller effects in the intervention groups and magnified effects in SSPT, exposing the trial to the risk that intervention effects were lost or underestimated.

Further research

Further research is warranted into factors that assist compliance, and into methods of monitoring compliance in this population. Investigations that consider whether age and intervention dose affect outcomes are also important. Studies are also needed to evaluate the responsiveness of the QUALEFFO-41 to rehabilitation interventions compared to other osteoporosis QoL instruments and to establish a formal MCID.

Conclusions and implications

The key messages are that at the main endpoint at one year the trial did not find significant benefits in favour of exercise or manual therapy over a single session of physiotherapy education for the primary outcomes of quality of life or back extensor strength. Several measures showed benefit at 4-months and some benefits persisted at 12-months. Whilst there is not adequate evidence to support a short programme of manual therapy or exercise therapy for long-term benefit it is arguable that short-term benefits are valuable and that education with a physiotherapist confers benefit.

Acknowledgements

Contributions of Authors

Karen L Barker (Professor of Physiotherapy) Chief Investigator, : Conceived and designed the study and had overall responsibility for the study design and delivery. She is the guarantor.

Meredith Newman (Research Fellow) Trial lead, trial design, development of interventions, supervision, writing and reviewing report.

Nigel Stallard (Statistician) Designing and conducting statistical analysis, writing and reviewing report.

Jose Leal (Health Economist) Designing and conducting economic analysis, supervision, writing and reviewing report.

Catherine Minns Lowe (Research Associate, Qualitative): Qualitative study design and conduct, writing and reviewing report.

Muhammad K Javaid (Associate Professor, Consultant in metabolic bone disease) Trial supervision, trial design, assessment of adverse events, reviewing report.

Angela Noufaily (Statistician) Conducting statistical analysis, writing and reviewing report.

Anish Adhikari (Health Economist) Economic analysis, writing and reviewing report

Tamsin Hughes (Research Physiotherapist) Trial intervention and assessments, writing and reviewing report.

David J Smith (Trial co-ordinator) Trial management, writing and reviewing report.

Varsha Gandhi (Trial co-ordinator): Trial management, quality assurance of interventions, trial management, writing and reviewing report.

Cyrus Cooper (Professor of Rheumatology) Trial conception and design, trial supervision, writing and reviewing report.

Sarah E Lamb (Professor of Rehabilitation; Director of Clinical Trials Unit): Trial conception and design, trial supervision, writing and reviewing report.

The Trial Steering Committee: Professor Maria Stokes (chairperson), Professor Sarah Lamb, Dr Victoria Allgar, Dr Allison Rushton, Dr Jane Simmonds, Dr Fiona Cramp, Mrs Jane Aldridge (patient representative)

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Competing Interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work, other than funding arrangements for the trial described in body of the text; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Transparency

The lead author (KLB) affirms that the manuscript is an honest, accurate and transparent account of the study being reported.

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