Cost-effectiveness of cognitive behavioural and personalised exercise interventions for reducing fatigue in inflammatory rheumatic diseases

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17. See supplementary material

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Keywords: cost-effectiveness, cognitive behavioural, personalised exercise, inflammatory rheumatic diseases, fatigue, remote delivery

Key messages:

- This study strengthens the economic evidence base for management of fatigue using non-pharmacological approaches
- Personalised exercise programmes accompanied by usual care are likely to be the most effective amongst all interventions, thus a cost-effectiveness option
- Cognitive behavioural approach produces very little additional benefit over usual care
Abstract

Objectives

To estimate the cost-effectiveness of a Cognitive Behavioural Approach (CBA) or a Personalised Exercise Programme (PEP), alongside usual care (UC), in patients with Inflammatory Rheumatic Diseases who report chronic, moderate to severe, fatigue.

Methods

A within-trial cost-utility analysis, was conducted using individual patient data collected within a multi-centre, three-arm randomised controlled trial over a 56-week period. The primary economic analysis was conducted from the UK National Health Service (NHS) perspective. Uncertainty was explored using cost-effectiveness acceptability curves and sensitivity analysis.

Results

Complete-case analysis showed that, compared with UC, both PEP and CBA were more expensive [adjusted mean cost difference: PEP £569 (95%CI £464 to £665), CBA £845 (95%CI £717 to £993)] and, in the case of PEP, significantly more effective [adjusted mean QALY difference: PEP 0.043 (95% CI 0.019 to 0.068), CBA 0.001 (95% CI -0.022 to 0.022)]. These led to an incremental cost-effectiveness ratio (ICER) of £13,159 for PEP vs. UC, and £793,777 for CBA vs. UC. Non-parametric bootstrapping showed that, at a threshold value of £20,000 per QALY gained, PEP had a probability of 88% of being cost-effective. In multiple imputation analysis, PEP was associated with significant incremental costs of £428 (95% CI £324 to £511) and a non-significant QALY gain of 0.016 (95% CI -0.003 to 0.035), leading to an ICER of £26,822 vs. UC. The estimates from sensitivity analyses were consistent with these results.

Conclusion

The addition of a PEP alongside UC is likely to provide a cost-effective use of health care resources.
Introduction

Inflammatory rheumatic diseases (IRDs) are a common group of chronic diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and axial spondyloarthritis (AxSpA). Together, they impose a large burden on patients and health care systems, with impacts driven largely by the accompanying symptoms of fatigue: in RA, up to 80% of patients report significant fatigue [1], leading to impaired quality of life (QOL) [2, 3] and work disability [4, 5]. For other IRDs, fatigue prevalence is similar, ranging from between 66%–85% [6, 7], and impacts on QOL and employment are equally pronounced [8-10]. A major problem however is that the patient experience with clinical management of fatigue is sub-optimal [11, 12]. There is now, however, growing recognition that non-pharmacological interventions, specifically cognitive-behavioural approaches (CBAs) and programmes designed to support increased physical activity, can improve fatigue and health-related QOL [13-16].

In addition to establishing the effectiveness of non-pharmacological interventions to manage fatigue, it is important to assess the cost-effectiveness of these interventions [17]. Scarcity of health care resources requires informed choices to be made between multiple competing demands. The use of economic criteria can inform these decisions and address the question of whether any additional gains in health are worth the levels of extra health care resources required. Previously, only a single cost-effectiveness analysis has been reported for fatigue in similar clinical populations and this was limited to CBA [18]. The aim of this paper therefore was to extend the evidence-base by reporting the results from an implementation trial that was conducted to assess the cost-effectiveness of the addition of either a CBA or a Personalised Exercise Programme (PEP) to usual care (UC), versus UC alone, in patients with IRDs who report chronic, moderate to severe, fatigue. Novel, potentially cost-saving features of these interventions included delivery by a) telephone rather than face-to-face and b) the local rheumatology health professional team rather than specialist clinical psychologists.

Methods

Study design

A within-trial economic evaluation was conducted alongside the Lessening the Impact of Fatigue in Inflammatory Rheumatic (LIFT) trial. LIFT is a multicentre, three-arm randomised controlled trial...
investigating the clinical effectiveness of the addition of either CBA or PEP to UC, versus UC alone, in reducing the impact and severity of fatigue for patients with IRD over a 56-week period. The primary economic analysis was conducted from the UK National Health Service (NHS) perspective. The UK NHS provides public healthcare that is free at the point of use. A total of 368 participants were included in the trial and randomised into three treatment groups: PEP (n=124), CBA (n=121) and UC (n=122). The randomised groups were similar at baseline – mean (SD) age was 56.4 (12.3) in PEP, 59.3 (13.0) in CBA and 56.8 (12.7) in UC, whilst mean Chalder Fatigue Scale (SD) was 21.4 (5.6) in PEP, 20.4 (5.8) in CBA and 20.7 (5.2) in UC. Full details of the LIFT trial have been published elsewhere [19, 20].

The trial, including this economic analysis, was approved by Wales Research Ethics Committee (REC) 7 (17/WA/0065); trial registration number (NCT03248518). All participants gave written informed consent at the baseline visit.

**Resource use and costs**

Data on health service resource use were assessed using participants’ cost diaries at baseline, 10-, 28- and 56-weeks post-baseline. Visits and/or telephone contacts to NHS primary and secondary care as well as participants’ out-of-pocket expenses were collected from participants’ entries in the cost diaries. Out-of-pocket expenses included private care visits, complementary medicines, over-the-counter medicines and additional expenses for any activities, aids and assistance. Information on time off work was captured to estimate productivity loss.

Fatigue-related resource use was valued using unit costs from published UK sources [21,22]. Gross age- and sex-specific wage rates obtained from the Annual Survey of Hours and Earnings, published by the Office for National Statistics (ONS), were used to value time lost from paid employment. Unpaid work was costed using the published value of unpaid work by the ONS, whilst forgone leisure time was valued using the value of non-working time obtained from the Department of Transport [23-25]. All costs were reported in 2019/2020 prices. Unit costs were adjusted for inflation where necessary using the NHS Cost Inflation Index [22]. The unit costs used to value the health service resource use and time loss are reported in Supplementary Table S1 (available at Rheumatology online).

**Interventions and cost**

All participants in the LIFT trial received UC and a Versus Arthritis education booklet for self-management of fatigue. The booklet consists of topics: fatigue validation, energy management,
priorities, sleep, stress and assertiveness, underpinned by goal setting and self-monitoring of activity. This is available in almost all UK rheumatology clinics, hence representing routine care in the UK.

Participants in the CBA and PEP group received up to seven one-to-one telephone sessions over 14 weeks with a trained therapist. The first PEP session was conducted face-to-face. Each session was scheduled to last up to 45 minutes. The trained therapists were rheumatology specialist physiotherapists for PEP, whilst rheumatology nurses, or qualified and trained allied health professionals, delivered CBA by telephone. A booster session was delivered at 22 weeks after the therapy initiation. Participants also received additional leaflets/information and diaries to assist with the intervention. All staff delivering trial interventions were supervised by a senior colleague.

The intervention cost was estimated by including the time spent on manual preparation, training sessions, delivering therapy sessions and supervision. The number of sessions and time spent on preparing, delivering and reviewing each session were obtained from therapist logs. The unit cost of trainers’ and therapists’ time was based on job title and grade. Consumable costs and expenses incurred during training sessions were included. Missing therapist time was imputed using mean imputation.

Health outcomes

Intervention effectiveness was measured by quality-adjusted life years (QALYs). Utility scores were estimated using participant responses to the Short Form-12 (SF-12) questionnaire at baseline and at each follow-up. Conversion of SF-12 responses to Short Form-Six Dimension (SF-6D) values was undertaken using a published UK tariff [26]. These utility scores were used to estimate QALYs over the 56-week period using the Area Under the Curve method. To assess wider impacts on well-being, effects were also measured using the ICECAP-A instrument [27], as well as changes in overall life satisfaction.

Analysis

The analysis was conducted on an intention-to-treat (ITT) basis using participant-level trial data. The planned primary analysis included participants with complete cost and SF-6D data at each timepoint. However, only 156 participants (42%) had complete data. Given the high proportion of missing data (58%), multiple imputation (MI) was also conducted alongside the primary analysis, as complete case analysis could introduce bias, unless data were missing completely at random.

To estimate differences in mean costs and QALYs between groups, generalised linear models with adjustment for minimisation factors (age, gender baseline Chalder Fatigue Scale score, the presence of...
depressive symptoms), baseline cost and baseline utility score were performed. Using the modified Park

test, Pearson’s correlation, Preigibon link and modified Hosmer-Lemeshow tests, a Gaussian family with

power 0.25 link function and a Poisson family with identity link function were specified for the cost and

QALY data, respectively [28]. Recycled predictions were used to recover adjusted mean costs and QALYs

by treatment allocation group and incremental differences between groups. Incremental cost-
effectiveness ratio (ICER) was calculated using the difference in mean cost divided by the difference in

mean QALYs.

Assuming missingness at random, missing data were addressed using MI by chained equations (MICE)

with predictive mean matching (kth-nearest neighbour=5) to generate 60 imputed data sets. The
imputation model was fitted with minimisation factors, the number of sessions attended and total
therapist time. Missing aggregated cost at the main cost categories level and SF-6D data were imputed
at each time point. Rubin’s rule was applied to obtain the pooled estimates across the imputed data
sets. Variance surrounding the incremental costs and QALYs was characterised using non-parametric
bootstrapping (1,000 iterations), with MICE (m=5) nested within the bootstrap loops [29].

Cost-effectiveness acceptability curves (CEACs) were constructed, using 1000 replications of each ICER,
to determine the probability of the alternative interventions being considered cost-effective at different
willingness to pay (WTP) per QALY thresholds (£20,000-£30,000 per QALY was used as these are the
commonly applied ceiling ratios in the UK). All analyses were undertaken using STATA version 15.0.

Sensitivity analysis

A number of sensitivity analyses were undertaken to explore the impact of uncertainty in estimates: (i)
applying a different intervention cost more reflective of future resource use in a steady state following
longer term roll-out of the CBA and PEP programmes; (ii) adopting a broader cost perspective by
including patient costs (out-of-pocket expenses and productivity loss); (iii) using ICECAP tariff as the
measure of effectiveness; and (iv) including only participants who attended ≥ 3 sessions. Several
assumptions were made to estimate the intervention costs at steady state: (i) therapist and participant
manuals would be reviewed and updated every 5 years; (ii) a yearly refresher training course would take
place for existing and new therapists; and (iii) no supervision for PEP therapists, and supervision time
reduced for CBA therapist to half of that in the trial.

Additional ad-hoc exploratory analyses were conducted to aid interpretation of study findings and to
inform future research. These included: (i) logistic regression analysis of the predictors of intervention
compliance; (ii) analysis to investigate the effect of changes in SF-6D domain score on overall SF-6D utility score change. The predictors associated with the change in SF-6D utility score from baseline to 56 weeks were identified from the coefficient of a change dummy of each SF-6D domain using linear regression, controlling for minimisation factors.

Results

Resource use and costs

The mean resource use and associated unadjusted costs per participant by treatment allocation group over 52 weeks follow-up are presented in Table 1. Considering primary care resource use frequency, the largest differences were seen for GP surgery visits and pharmacy visits. Compared with UC, fewer participants in PEP and CBA groups had GP surgery visits (8% PEP vs. 10% CBA vs. 17% UC), and both intervention groups also had a lower average number of visits (0.30 PEP vs. 0.29 CBA vs. 0.51 UC). Fewer PEP and CBA participants had pharmacist visits (3% PEP vs. 6% CBA vs. 14% UC), and there was also a lower average number of pharmacist visits amongst participants randomised to the interventions compared with usual care (0.12 PEP vs. 0.17 CBA vs. 0.80 UC). The average GP surgery visit costs by treatment allocation were £12, £11 and £20 for PEP, CBA and UC, respectively. The average pharmacist visit costs by treatment allocation were £1, £1 and £7 for PEP, CBA and UC, respectively. In terms of hospital resource use, the largest differences were observed in outpatient visits, with fewer participants in the PEP and UC groups attending compared with those in the CBA group (12% PEP vs. 17% CBA vs. 12% UC respectively), leading to outpatient visit costs of £64, £79 and £72 respectively. Patient cost differences were also seen, with participants in both intervention groups experiencing lower costs than usual care (£267 PEP vs. £302 CBA vs. £323 UC).

Overall, both PEP and CBA groups had lower total average costs for NHS primary and secondary care and patient costs than that of UC group, owing to the lower proportion of resource users and the amount used for each resource type. This suggests some cost savings associated with PEP and CBA, although these were modest in comparison to the respective intervention costs of £459 and £717 per patient. Including intervention costs, the complete resource use data over 52 weeks was estimated to produce total average unadjusted NHS (NHS + patient) costs of £669 (£934), £924 (£1219) and £139 (£459) in the PEP, CBA and UC groups, respectively. Compared with UC, this produced an unadjusted NHS cost difference of £530 for PEP and £785 for CBA.
Compared with PEP, a higher proportion of participants in the CBA group completed three or more sessions (75% vs. 61%), and a higher proportion of CBA participants fully completed all 8 sessions (60% vs. 40%). Based on ITT analysis, the average time spent on each session by therapists was longer in CBA than that of PEP, resulting in higher total average therapy delivery time per participant for the CBA group (483 minutes vs. 324 minutes) (Supplementary Table S2. Available at Rheumatology online).

Including other costs such as training and supervision, unadjusted average intervention costs were higher in the CBA group than the PEP group (£717 vs. £459), predominantly driven by therapy delivery costs. A breakdown of intervention costs per participant is presented in Supplementary Table S3 (available at Rheumatology online).

Health outcomes

The mean health outcome scores at each follow-up and mean total scores over 52 weeks are summarised in Table 2. At baseline, there was a small, non-significant difference in unadjusted SF-6D and ICECAP scores in favour of CBA group. The mean unadjusted scores for all health outcomes (SF-6D, ICECAP-A and life satisfaction) at 10-, 28- and 56-weeks follow-up were higher in the PEP and CBA groups. Compared with UC, a higher unadjusted QALY difference was seen for both intervention groups (0.037 PEP vs. 0.019 CBA for QALY difference), indicating better health. However, after adjusting for baseline utility and other minimisation factors, Table 3 shows that, relative to CBA, a higher adjusted QALY gain was observed for PEP against UC under both complete-case analysis (=0.043 QALY gain) and MI analysis (=0.016).

Cost-utility analysis

Compared with UC, results from the complete-case analysis showed that both PEP and CBA were more expensive [adjusted mean cost difference: PEP £569 (95% CI £464 to £665), CBA £845 (95% CI £717 to £993)] and, in the case of PEP, significantly more effective [adjusted mean QALY difference: PEP 0.043 (95% CI 0.019 to 0.068), CBA 0.001 (95% CI -0.022 to 0.022)]. These led to an ICER of £13,159 for PEP vs. UC, and £793,777 for CBA vs. UC. When comparing PEP against CBA, PEP was found to dominate CBA as PEP was associated with lower total mean costs and higher total mean QALYs gained (Table 3). The non-parametric bootstrapping results showed that, at a WTP threshold of £20,000 per QALY gained, PEP was found to have 88% chance of being the preferred intervention (Figure 1).
The imputed dataset yielded lower mean costs and mean QALYs across all groups, thus the difference in total mean costs and total mean QALYs was reduced. Compared with UC, PEP was associated with significantly higher costs of £428 (95% CI £324 to £511) but a non-significant higher QALY gain of 0.016 (95% CI -0.003 to 0.035), leading to an ICER of £26,822. For CBA, the adjusted QALY difference of 0.006 was in favour of UC, thus CBA was dominated (Table 3). The non-parametric bootstrapping results showed that, at a WTP threshold of £20,000 per QALY gained, UC was found to have a 67% chance of being the preferred intervention (Figure 1). Cost-effectiveness scatterplots are available in Supplementary Figure S1 (available at *Rheumatology* online).

**Sensitivity analyses**

Most of the results of the sensitivity analyses were consistent with the main cost-effectiveness findings that used MI (Table 4). The results were sensitive to the proportion of participants that completed three or more sessions (hereafter referred to as compliers). The analysis including compliers only yielded an ICER of £17,994 for PEP vs. UC. Further, the additional cost per QALY gained for PEP was slightly reduced to £21,129 when interventions were costed under steady state assumptions. Based on non-parametric bootstrapping results using compliers only, both PEP and UC were found to have a 50% chance of being the preferred intervention at the WTP threshold of £20,000 per QALY gained (Supplementary Figure S2. Available at *Rheumatology* online).

Supplementary Table S4A (available at *Rheumatology* online) demonstrates that none of the minimisation factors or baseline variables were predictive of participants undertaking three or more sessions. However, there was some evidence that men may be more likely to undertake two sessions or less if they received CBA (p=0.05).

Supplementary Table S4B (available at *Rheumatology* online) shows that, for PEP participants, a one level shift in SF-6D domain was associated with positive change in SF-6D utility score, indicating improved quality of life across all domains. Social functioning was the largest domain found to be significantly correlated with changes in SF-6D score (coefficient = 0.051, p <0.05). In the CBA group, the shift in five SF-6D domains was associated with non-significant, negative change in SF-6D score. For the vitality domain, an explicit surrogate of fatigue, the association with the SF-6D change score was similar between PEP and CBA, whilst a larger association was seen for the UC group.

**Discussion**
This economic evaluation builds on our earlier published results from LIFT trial which demonstrated CBA and PEP provide clinically important improvements in fatigue [19]. For decision-makers applying a WTP threshold of £20,000 per QALY gained to judge the cost-effectiveness of the interventions, there was a marked difference in costs and QALYs between both interventions, with PEP providing greater benefits in health-related QOL for lower health care and total societal costs than CBA.

The results from the LIFT trial using fatigue as the primary health outcome are largely consistent with the findings here in terms QALY gains, where both interventions were found to be effective in reducing the symptoms of fatigue, although larger effects were observed for PEP. However, we report almost zero gain in health-related QOL arising from the CBA intervention. One potential explanation for this finding might relate to differences in compliance between the groups; for example, whilst the level of compliance was found to be somewhat higher with CBA than with PEP, there may exist other characteristics that mitigate against improvements with either intervention, such as differences in baseline levels of employment or, disease. Although an additional ad-hoc exploratory analyses failed to identify such factors, the analysis was underpowered and the variation in compliance could be explained by unrecorded measures of health. Alternatively, the CBA approach may do less well than PEP at targeting the most important individual domains of the SF-6D. This was also explored in an additional exploratory analysis, which focused on estimating the correlation between a change in individual SF-6D domains and overall SF-6D values. For CBA this revealed that a change in domains was not associated with significant changes in overall SF-6D value, whilst for PEP, there was a significant positive correlation with social functioning. This is consistent with a significant positive change in work activity and valued activities for PEP reported earlier [19], suggesting that PEP was more effective than CBA in helping patients return to work, be more productive whilst at work, or to re-engage with their usual activities. A final explanation might relate to levels of missing data. However, the results were found to be robust after conducting analysis with both complete cases as well as MI.

It is challenging to compare our study with previously published literature, as there is a very limited evidence base on the cost-effectiveness of non-pharmacological therapies (specifically, CBA vs. PEP) for managing fatigue in similar populations to those under consideration here. One exception is the economic analysis conducted as part of the RAFT trial [18]. This found that a group CBT programme delivered by rheumatology tutor pairs (nurses and occupational therapists) was associated with a non-significant cost increase (mean cost per patient of £434 (95% CI -£389 to £1258) and a non-significant QALY difference (QALY gain per patient of 0.008 (95% CI -0.008 to 0.023). The probability that the RAFT
programme was cost-effective relative to UC ranged between 28%-35% within the WTP threshold of £20,000-£30,000 per QALY gained. These results therefore suggest that, relative to individual therapy, group-based therapy can be expected to lead to use fewer health care resources. Economic evaluations of exercise are also rare in similar clinical populations [30]. However, a larger evidence-base is available in osteoarthritis and musculoskeletal conditions, where exercise is shown to be a cost-effective use of resources [31].

The economic evaluation reported here is associated with some potential limitations. First, due to missing data, there remains some level of uncertainty in the results, with MI leading to greater uncertainty regarding whether PEP remains cost-effective at a WTP threshold of £20,000 per QALY gained. Any future study therefore should aim to test different data collection strategies (e.g., web-based links, SMS texts) in order to minimise levels of missing data and improve participant retention. Second, future studies might wish to consider stratification based on patient preference, as randomisation to a less preferred strategy might de-motivate study participants in implementing health behaviour change and affect study retention [32]. Additionally, a number of benefits were observed for CBA and/or PEP including improved mental health related quality of life, sleep, enhanced value life activities, reduced levels of work disability and depression [19], however the quality of life measure used in the economic evaluation might fall short in capturing these values.

A strength of this evaluation is multi-centre nature of the study design. The interventions were implemented in six centres throughout the UK. Therefore, the economic analysis should be reasonably generalisable to similar sized centres across the UK, although further longer-term studies of implementation are warranted to test this hypothesis. In addition, the results from other measures of health and well-being were largely consistent with the SF-6D responses, suggesting that we did not omit any wider measures of benefit.

**Conclusion**

A PEP generated greater gains in health-related QOL than a CBA for the management of fatigue amongst patients with IRDs. Further, using conventional WTP for QALY gain thresholds, the addition of a PEP alongside UC alone is likely to provide a cost-effective use of health care resources.
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LIFT study group:

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**Disclosure statement:** The authors declare no conflicts of interest.

**Data availability statement**

Data of anonymised individual patient are available upon reasonable request made to the corresponding author, subject to a data sharing agreement and UK research governance regulations.
References


Med Care. 2004;42(9):851-859.


Table 1: Unadjusted mean resource use and costs per patient over 52 weeks follow-up

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<th>N</th>
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<th>Mean cost, £ (SD)</th>
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<th>Mean resource use (SD)</th>
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<td>66</td>
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<tr>
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<td>Practice nurse visits at surgery</td>
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<td>79</td>
<td>12 (10)</td>
<td>0.37 (1.55)</td>
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<td>66</td>
<td>5 (4)</td>
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<td>0.42 (1.92)</td>
<td>79</td>
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<td>0.09 (0.29)</td>
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<td>0 (0)</td>
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<td>Pharmacist visits</td>
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<td>79</td>
<td>17 (14)</td>
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<td>0.17 (0.54)</td>
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<td>0 (0)</td>
<td>0 (0)</td>
<td>79</td>
<td>4 (3)</td>
<td>0.10 (0.59)</td>
<td>1.44 (8.38)</td>
<td>66</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<td>0 (0)</td>
<td>0 (0)</td>
<td>79</td>
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<td>66</td>
<td>0 (0)</td>
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</table>

a Includes preparation, training, intervention delivery and therapist supervision

b Sum of therapist time (in mins) on preparing, delivering and reviewing the sessions. Missing therapist time was imputed using mean imputation
<table>
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<tr>
<th>Service Type</th>
<th>Count</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Count</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Count</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
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<td>Community physiotherapist visits</td>
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<td>(0.40)</td>
<td>3.34</td>
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<td>0.03</td>
<td>(0.23)</td>
<td>1.61</td>
<td>66</td>
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<td>Community occupational therapist visits</td>
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<td>(0.16)</td>
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<td>Other community health professional visits</td>
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<td>0.80</td>
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<tr>
<td>Total NHS primary care costs</td>
<td>57</td>
<td>15 (12)</td>
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<td>22.89</td>
<td>79</td>
<td>35 (29)</td>
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<td>45.06</td>
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<td>19 (16)</td>
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<td>24.01</td>
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<td>NHS secondary care</td>
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<tr>
<td>NHS 24</td>
<td>57</td>
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<td>79</td>
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<td>0 (0)</td>
<td>66</td>
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<td>(0.12)</td>
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<td>Accident &amp; Emergency visits</td>
<td>57</td>
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<td>(0.19)</td>
<td>6.14</td>
<td>79</td>
<td>2 (2)</td>
<td>0.04</td>
<td>(0.25)</td>
<td>6.53</td>
<td>66</td>
<td>2 (2)</td>
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<tr>
<td>Outpatient clinic visits</td>
<td>57</td>
<td>15 (12)</td>
<td>0.43</td>
<td>(0.83)</td>
<td>64.18</td>
<td>79</td>
<td>15 (12)</td>
<td>0.49</td>
<td>(1.97)</td>
<td>72.03</td>
<td>66</td>
<td>20 (17)</td>
</tr>
<tr>
<td>Non-elective admission days</td>
<td>57</td>
<td>1 (1)</td>
<td>0.02</td>
<td>(0.13)</td>
<td>10.75</td>
<td>79</td>
<td>1 (1)</td>
<td>0.03</td>
<td>(0.23)</td>
<td>15.24</td>
<td>66</td>
<td>0 (0)</td>
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<tr>
<td>Total NHS hospital care costs</td>
<td>57</td>
<td>17 (14)</td>
<td>-</td>
<td>81.07</td>
<td>79</td>
<td>16 (13)</td>
<td>-</td>
<td>93.81</td>
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<td>20 (17)</td>
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<td>Patient cost</td>
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<td></td>
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<tr>
<td>Private health care professional/therapist visit</td>
<td>57</td>
<td>10 (8)</td>
<td>0.28</td>
<td>(0.70)</td>
<td>13.16</td>
<td>79</td>
<td>12 (10)</td>
<td>0.72</td>
<td>(2.49)</td>
<td>27.26</td>
<td>66</td>
<td>7 (6)</td>
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<tr>
<td>Complementary medicines</td>
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<td>14 (11)</td>
<td>-</td>
<td>20.74</td>
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<td>14 (11)</td>
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<td>7.34</td>
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<td>9 (7)</td>
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<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
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<td>--------------------------</td>
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<tr>
<td>Additional expenses</td>
<td>57 21 (17)</td>
<td>57.33 (127.63)</td>
<td>79 34 (28)</td>
<td>109.13 (263.30)</td>
<td>66 23 (19)</td>
<td>109.11 (268.30)</td>
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</tr>
<tr>
<td>Time/ productivity loss</td>
<td>56 11 (9)</td>
<td>179.74 (799.37)</td>
<td>78 13 (11)</td>
<td>178.52 (956.23)</td>
<td>65 4 (3)</td>
<td>134.07 (978.47)</td>
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<tr>
<td>Total patient costs</td>
<td>56 29 (23)</td>
<td>267.09 (821.25)</td>
<td>78 46 (38)</td>
<td>322.57 (1010.85)</td>
<td>65 28 (23)</td>
<td>301.88 (1096.114)</td>
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<tr>
<td><strong>Total NHS costs</strong></td>
<td>57 -</td>
<td>668.89 (268.79)</td>
<td>79 -</td>
<td>138.86 (441.09)</td>
<td>66 -</td>
<td>924.32 (317.35)</td>
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<td><strong>Total costs, including</strong></td>
<td>56 -</td>
<td>934.40 (931.51)</td>
<td>78 -</td>
<td>459.37 (1195.93)</td>
<td>65 -</td>
<td>1219.44 (1210.19)</td>
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</tbody>
</table>

**Abbreviations**

CBA, cognitive behavioural approach; NHS, National Health Service; PEP, personalised exercise programme; SD, standard deviation; UC, usual practice.
<table>
<thead>
<tr>
<th></th>
<th>PEP, n=124</th>
<th>UC, n=122</th>
<th>CBA, n=121</th>
</tr>
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<tbody>
<tr>
<td><strong>SF-6D utility score, N: mean (SD)</strong></td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>116: 0.579 (0.119)</td>
<td>117: 0.584 (0.102)</td>
<td>114: 0.598 (0.109)</td>
</tr>
<tr>
<td>10 weeks</td>
<td>89: 0.613 (0.135)</td>
<td>95: 0.603 (0.112)</td>
<td>92: 0.616 (0.116)</td>
</tr>
<tr>
<td>28 weeks</td>
<td>71: 0.634 (0.135)</td>
<td>80: 0.606 (0.102)</td>
<td>85: 0.615 (0.121)</td>
</tr>
<tr>
<td>56 weeks</td>
<td>73: 0.633 (0.132)</td>
<td>81: 0.596 (0.099)</td>
<td>86: 0.610 (0.116)</td>
</tr>
<tr>
<td>Total QALY over 52 weeks</td>
<td>55: 0.641 (0.106)</td>
<td>68: 0.604 (0.092)</td>
<td>72: 0.622 (0.106)</td>
</tr>
<tr>
<td><strong>ICECAP-A, n: mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>118: 0.728 (0.183)</td>
<td>116: 0.740 (0.181)</td>
<td>119: 0.762 (0.163)</td>
</tr>
<tr>
<td>10 weeks</td>
<td>89: 0.767 (0.173)</td>
<td>94: 0.761 (0.188)</td>
<td>93: 0.763 (0.183)</td>
</tr>
<tr>
<td>28 weeks</td>
<td>78: 0.793 (0.183)</td>
<td>82: 0.768 (0.184)</td>
<td>85: 0.777 (0.172)</td>
</tr>
<tr>
<td>56 weeks</td>
<td>76: 0.779 (0.177)</td>
<td>82: 0.745 (0.194)</td>
<td>89: 0.789 (0.178)</td>
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<tr>
<td>Total year of full capability over 52 weeks</td>
<td>58: 0.795 (0.158)</td>
<td>71: 0.762 (0.178)</td>
<td>79: 0.781 (0.166)</td>
</tr>
<tr>
<td><strong>Life satisfaction, n: mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>121: 4.405 (1.547)</td>
<td>120: 4.625 (1.512)</td>
<td>120: 4.533 (1.567)</td>
</tr>
<tr>
<td>10 weeks</td>
<td>91: 4.725 (1.450)</td>
<td>95: 4.716 (1.541)</td>
<td>92: 4.739 (1.511)</td>
</tr>
<tr>
<td>28 weeks</td>
<td>78: 4.795 (1.515)</td>
<td>82: 4.878 (1.469)</td>
<td>88: 4.830 (1.548)</td>
</tr>
<tr>
<td>56 weeks</td>
<td>76: 4.829 (1.455)</td>
<td>83: 4.434 (1.647)</td>
<td>88: 4.830 (1.540)</td>
</tr>
<tr>
<td>Total life satisfaction score over 52 weeks</td>
<td>61: 4.897 (1.201)</td>
<td>71: 4.717 (1.273)</td>
<td>80: 4.853 (1.338)</td>
</tr>
</tbody>
</table>

**Abbreviations**

CBA, cognitive behavioural approach; ICECAP-A, ICEpop CAPability measure for Adults; PEP, personalised exercise programme; QALY, quality-adjusted life year; SD, standard deviation; SF-6D, Short Form Six-Dimension; UC, usual practice.
Table 3: Adjusted\(^c\) mean incremental costs, incremental QALYs, and incremental cost-effectiveness ratio over 52 weeks between groups

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Mean costs, £ (95% CI)(^c)</th>
<th>Mean QALYs (95% CI)(^c)</th>
<th>Incremental mean costs, £ (95% CI)(^d,e)</th>
<th>Incremental mean QALYs (95% CI)(^d,e)</th>
<th>ICER (£/QALY)(^f)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete cases, n=156 (NHS perspective)(^g)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>UC</td>
<td>119.59 (54.60 to 197.53)</td>
<td>0.605 (0.588 to 0.623)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEP</td>
<td>688.96 (616.24 to 756.45)</td>
<td>0.649 (0.626 to 0.674)</td>
<td>569.36 (464.29 to 664.80)</td>
<td>0.043 (0.019 to 0.068)</td>
<td>13,159</td>
</tr>
<tr>
<td>CBA</td>
<td>964.46 (863.20 to 1082.24)</td>
<td>0.606 (0.586 to 0.629)</td>
<td>844.86 (717.25 to 993.97)</td>
<td>0.001 (-0.022 to 0.022)</td>
<td>Dominated</td>
</tr>
<tr>
<td>Imputed cases, n=367 (NHS perspective)(^h)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UC</td>
<td>119.65 (52.79 to 208.76)</td>
<td>0.603 (0.589 to 0.618)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEP</td>
<td>548.07 (486.22 to 596.50)</td>
<td>0.617 (0.599 to 0.636)</td>
<td>428.41 (324.37 to 510.83)</td>
<td>0.016 (-0.003 to 0.035)</td>
<td>26,822</td>
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<tr>
<td>CBA</td>
<td>843.79 (767.48 to 915.02)</td>
<td>0.596 (0.581 to 0.614)</td>
<td>724.13 (609.44 to 825.55)</td>
<td>-0.006 (-0.024 to 0.013)</td>
<td>Dominated</td>
</tr>
</tbody>
</table>

**Abbreviations**
CBA, cognitive behavioural approach; CI, confidence interval; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; PEP, personalised exercise programme; QALY, quality-adjusted life year; UC, usual practice.

\(^c\) Adjusted for baseline differences (age, gender, baseline Chalder Fatigue Scale score, HADS depression subscale >10 at baseline, baseline utility score, baseline cost and centre)
\(^d\) Bootstrapped non-parametric 95% confidence interval (2.5\(^{th}\)/97.5\(^{th}\) centile). Generalised linear model with Gaussian distribution and power 0.25 link function to estimate incremental costs and generalised linear model with Poisson distribution and identity link function to estimate incremental QALYs
\(^e\) Compared with usual care
\(^f\) ICER expressed relative to next less costly, non-dominated alternative
\(^g\) 156 complete cases were included - PEP (n=43), UC (n=63) and CBA (n=50). Complete cases are without any missing data on cost and health utility at each time point
\(^h\) Imputed dataset (n=60)
Table 4: Sensitivity analysis of incremental cost-effectiveness ratio over 52 weeks between groups using multiple imputation approach

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Mean costs, £ (95% CI)c</th>
<th>Mean QALYs (95% CI)c</th>
<th>Incremental mean costs, £ (95% CI)d,e</th>
<th>Incremental mean QALYs (95% CI)d,e</th>
<th>ICER (£/QALY)f</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using intervention cost when the programme reaches a steady state, n=367 (NHS perspective)h,i</td>
<td></td>
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</tr>
<tr>
<td>UC</td>
<td>119.67 (52.74 to 209.38)</td>
<td>0.601 (0.587 to 0.616)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PEP</td>
<td>457.15 (392.22 to 505.64)</td>
<td>0.617 (0.599 to 0.636)</td>
<td>337.47 (234.35 to 419.91)</td>
<td>0.016 (-0.003 to 0.035)</td>
<td>21,129</td>
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<tr>
<td>CBA</td>
<td>773.99 (697.98 to 846.27)</td>
<td>0.595 (0.578 to 0.612)</td>
<td>654.32 (538.45 to 756.10)</td>
<td>-0.006 (-0.024 to 0.013)</td>
<td>Dominated</td>
</tr>
<tr>
<td>Including patient costs, n=367 (NHS perspective)h,j</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UC</td>
<td>304.96 (198.83 to 416.06)</td>
<td>0.602 (0.588 to 0.617)</td>
<td></td>
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<td></td>
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<tr>
<td>PEP</td>
<td>786.90 (667.34 to 921.96)</td>
<td>0.616 (0.597 to 0.635)</td>
<td>481.94 (346.64 to 617.33)</td>
<td>0.014 (-0.006 to 0.033)</td>
<td>35,424</td>
</tr>
<tr>
<td>CBA</td>
<td>1103.95 (950.45 to 1250.58)</td>
<td>0.596 (0.579 to 0.613)</td>
<td>798.88 (661.75 to 932.95)</td>
<td>-0.006 (-0.023 to 0.012)</td>
<td>Dominated</td>
</tr>
<tr>
<td>Using ICECAP-A utility score, n=367 (NHS perspective)h</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>UC</td>
<td>121.91 (54.10 to 221.56)</td>
<td>0.756 (0.729 to 0.782)</td>
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</tr>
<tr>
<td>PEP</td>
<td>558.48 (495.84 to 604.66)</td>
<td>0.776 (0.748 to 0.803)</td>
<td>436.57 (330.21 to 521.89)</td>
<td>0.019 (-0.011 to 0.055)</td>
<td>22,915</td>
</tr>
<tr>
<td>CBA</td>
<td>847.40 (773.13 to 918.20)</td>
<td>0.750 (0.725 to 0.775)</td>
<td>725.49 (608.37 to 825.11)</td>
<td>-0.006 (-0.034 to 0.025)</td>
<td>Dominated</td>
</tr>
</tbody>
</table>

i Lower intervention costs were applied - PEP £368, CBA £647
j Generalised linear model with Poisson distribution and power 0.5 link function to estimate incremental costs and generalised linear model with Gamma distribution and identity link function to estimate incremental QALYs
Including compliant participants, n=287 (NHS perspective)\(^k\)

<table>
<thead>
<tr>
<th></th>
<th>UC</th>
<th>CI</th>
<th>PEP</th>
<th>CI</th>
<th>CBA</th>
<th>CI</th>
<th>ICER</th>
<th>(%) Difference</th>
<th>Dominated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>118.92 (54.41 to 208.22)</td>
<td>0.603 (0.588 to 0.618)</td>
<td>583.63 (470.77 to 667.64)</td>
<td>0.032 (0.013 to 0.054)</td>
<td>17,994</td>
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<tr>
<td></td>
<td>702.55 (648.29 to 755.44)</td>
<td>0.635 (0.616 to 0.656)</td>
<td>583.63 (470.77 to 667.64)</td>
<td>0.032 (0.013 to 0.054)</td>
<td>17,994</td>
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<td>985.45 (933.48 to 1052.49)</td>
<td>0.605 (0.589 to 0.618)</td>
<td>866.52 (769.14 to 960.42)</td>
<td>0.002 (-0.017 to 0.019)</td>
<td>Dominated</td>
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</tr>
</tbody>
</table>

**Abbreviations**

CBA, cognitive behavioural approach; CI, confidence interval; ICECAP-A, ICEpop CAPability measure for Adults; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; PEP, personalised exercise programme; QALY, quality-adjusted life year; UC, usual practice.

\(^k\) Participants were deemed as compliant to the intervention if ≥3 PEP/CBA sessions were attended. A total of 287 cases were included - PEP (n=75), UC (n=122) and CBA (n=90)
Complete cases, n=156

Imputed dataset, n=367

Abbreviations
CBA, cognitive behavioural approach; NHS, National Health Service; PEP, personalised exercise programme; UC, usual care.

Figure 1: Cost-effectiveness acceptability curves of base case analysis (NHS perspective)
Abbreviations
CBA, cognitive behavioural approach; NHS, National Health Service; PEP, personalised exercise programme; UC, usual care.

117x45mm (300 x 300 DPI)