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Clinical science

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

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## Abstract

**Objectives:** To estimate the cost-effectiveness of a cognitive behavioural approach (CBA) or a personalized 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 multicentre, three-arm randomized 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, £665); CBA £845 (95% CI: £717, £993)] and, in the case of PEP, significantly more effective [adjusted mean quality-adjusted life year (QALY) difference: PEP 0.043 (95% CI: 0.019, 0.068); CBA 0.001 (95% CI: −0.022, 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, £511) and a non-significant QALY gain of 0.016 (95% CI: −0.003, 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.

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

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**Rheumatology key messages**

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

## Introduction

Inflammatory rheumatic diseases (IRDs) are a common group of chronic diseases, including RA, SLE and axial spondyloarthritis. 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 between 66 and 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 suboptimal [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 personalized exercise programme (PEP) to usual care (UC), *vs* UC alone, in patients with IRDs who report chronic, moderate to severe fatigue. Novel, potentially cost-saving features of these interventions included delivery by (i) telephone rather than face-to-face and (ii) 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 randomized controlled trial investigating the clinical effectiveness of the addition of either CBA or PEP to UC, *vs* 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 randomized into three treatment groups: PEP ($n = 124$), CBA ($n = 121$) and UC ($n = 122$). The randomized groups were similar at baseline—mean (S.D.) age was 56.4 (12.3) in PEP, 59.3 (13.0) in CBA and 56.8 (12.7) in UC, while mean Chalder Fatigue Scale (S.D.) 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, were used to value time lost from paid employment. Unpaid work was costed using the published value of unpaid work by the Office for National Statistics, while 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 the 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 min. The trained therapists were rheumatology specialist physiotherapists for PEP, while rheumatology nurses, or qualified and trained allied health professionals, delivered CBA by telephone. A booster session was delivered at 22 weeks after the therapy

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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 basis using participant-level trial data. The planned primary analysis included participants with complete cost and SF-6D data at each time point. 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, generalized linear models with adjustment for minimization 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 test, 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 ($k$th-nearest neighbour = 5) to generate 60 imputed data sets. The imputation model was fitted with minimization 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 characterized using non-parametric bootstrapping (1000 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 (StataCorp LLC, College Station, TX, USA).

### 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 $\geq$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 and (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 minimization 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 among participants randomized 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), leading to outpatient visit costs of £64 PEP, £79 CBA and £72 UC, respectively. Patient cost differences were also seen, with

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

| Resource use item | PEP ($n = 124$) | | | | UC ($n = 122$) | | | | CBA ($n = 121$) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | Users, *n* (%) | Resource use[b], mean (S.D.) | Cost, mean (S.D.), £ | *n* | Users, *n* (%) | Resource use, mean (S.D.) | Cost, mean (S.D.), £ | *N* | Users, *n* (%) | Resource use, mean (S.D.) | Cost, mean (S.D.), £ |
| Intervention[a] | 124 | 104 (84) | 323.85 (234.29) | 459.15 (211.45) | 122 | 0 (0) | 0 (0) | 0 (0) | 121 | 103 (85) | 483.45[b] (289.70) | 717.32 (269.09) |
| NHS primary care | | | | | | | | | | | | |
| GP visits at surgery | 57 | 10 (8) | 0.30 (0.76) | 11.83 (29.94) | 79 | 21 (17) | 0.51 (1.22) | 20.08 (48.30) | 66 | 12 (10) | 0.29 (0.80) | 11.41 (31.69) |
| GP telephone consultations | 57 | 3 (2) | 0.09 (0.43) | 2.68 (13.26) | 79 | 14 (11) | 0.19 (0.43) | 5.80 (13.00) | 66 | 4 (3) | 0.08 (0.32) | 2.31 (9.74) |
| GP home visits | 57 | 0 (0) | 0 (0) | 0 (0) | 79 | 0 (0) | 0 (0) | 0 (0) | 66 | 0 (0) | 0 (0) | 0 (0) |
| Practice nurse visits at surgery | 57 | 6 (5) | 0.26 (0.88) | 3.71 (12.37) | 79 | 12 (10) | 0.37 (1.55) | 5.18 (21.93) | 66 | 5 (4) | 0.20 (0.79) | 2.78 (11.13) |
| Practice nurse telephone consultations | 57 | 3 (2) | 0.07 (0.32) | 0.42 (1.92) | 79 | 7 (6) | 0.09 (0.29) | 0.53 (1.72) | 66 | 3 (2) | 0.05 (0.21) | 0.27 (1.26) |
| Practice nurse home visits | 57 | 0 (0) | 0 (0) | 0 (0) | 79 | 0 (0) | 0 (0) | 0 (0) | 66 | 1 (1) | 0.02 (0.12) | 0.46 (3.76) |
| Pharmacist visits | 57 | 4 (3) | 0.12 (0.57) | 0.91 (4.18) | 79 | 17 (14) | 0.80 (2.38) | 7.03 (30.53) | 66 | 7 (6) | 0.17 (0.54) | 1.00 (3.36) |
| Pharmacist telephone consultations | 57 | 0 (0) | 0 (0) | 0 (0) | 79 | 4 (3) | 0.10 (0.59) | 1.44 (8.38) | 66 | 0 (0) | 0 (0) | 0 (0) |
| Pharmacist home visits | 57 | 0 (0) | 0 (0) | 0 (0) | 79 | 1 (1) | 0.01 (0.11) | 0.39 (3.44) | 66 | 0 (0) | 0 (0) | 0 (0) |
| Community physiotherapist visits | 57 | 1 (1) | 0.05 (0.40) | 3.34 (25.20) | 79 | 1 (1) | 0.03 (0.23) | 1.61 (14.27) | 66 | 1 (1) | 0.09 (0.74) | 5.77 (46.84) |
| Community occupational therapist visits | 57 | 0 (0) | 0 (0) | 0 (0) | 79 | 2 (2) | 0.03 (0.16) | 2.21 (13.82) | 66 | 0 (0) | 0 (0) | 0 (0) |
| Other community health professional visits | 57 | 0 (0) | 0 (0) | 0 (0) | 79 | 1 (1) | 0.01 (0.11) | 0.80 (7.14) | 66 | 0 (0) | 0 (0) | 0 (0) |
| Total NHS primary care costs | 57 | 15 (12) | — | 22.89 (49.98) | 79 | 35 (29) | — | 45.06 (107.76) | 66 | 19 (16) | — | 24.01 (63.12) |
| NHS secondary care | | | | | | | | | | | | |
| NHS 24 | 57 | 0 (0) | 0 (0) | 0 (0) | 79 | 0 (0) | 0 (0) | 0 (0) | 66 | 1 (1) | 0.02 (0.12) | 0.21 (1.73) |
| Accident & Emergency visits | 57 | 2 (2) | 0.04 (0.19) | 6.14 (32.22) | 79 | 2 (2) | 0.04 (0.25) | 6.53 (43.06) | 66 | 2 (2) | 0.03 (0.17) | 5.21 (29.72) |
| Outpatient clinic visits | 57 | 15 (12) | 0.43 (0.83) | 64.18 (124.00) | 79 | 15 (12) | 0.49 (1.97) | 72.03 (291.58) | 66 | 20 (17) | 0.53 (1.03) | 79.41 (153.66) |
| Non-elective admission days | 57 | 1 (1) | 0.02 (0.13) | 10.75 (80.46) | 79 | 1 (1) | 0.03 (0.23) | 15.24 (135.48) | 66 | 0 (0) | 0 (0) | 0 (0) |
| Total NHS hospital care costs | 57 | 17 (14) | — | 81.07 (155.93) | 79 | 16 (13) | — | 93.81 (351.64) | 66 | 20 (17) | — | 84.84 (161.67) |
| Patient cost | | | | | | | | | | | | |
| Private health care professional/therapist visit | 57 | 10 (8) | 0.28 (0.70) | 13.16 (43.07) | 79 | 12 (10) | 0.72 (2.49) | 27.26 (89.51) | 66 | 7 (6) | 0.70 (3.00) | 32.68 (168.24) |
| Complementary medicines | 57 | 14 (11) | — | 20.74 (63.00) | 79 | 14 (11) | — | 7.34 (21.27) | 66 | 9 (7) | — | 25.65 (146.46) |
| Additional expenses | 57 | 21 (17) | — | 57.33 (127.63) | 79 | 34 (28) | — | 109.13 (263.30) | 66 | 23 (19) | — | 109.11 (268.30) |
| Time/productivity loss | 56 | 11 (9) | — | 179.74 (799.37) | 78 | 13 (11) | — | 178.52 (956.23) | 65 | 4 (3) | — | 134.07 (978.47) |
| Total patient costs | 56 | 29 (23) | — | 267.09 (821.25) | 78 | 46 (38) | — | 322.57 (1010.85) | 65 | 28 (23) | — | 301.88 (1096.114) |
| Total NHS costs | 57 | — | — | 668.89 (268.79) | 79 | — | — | 138.86 (441.09) | 66 | — | — | 924.32 (317.35) |
| Total costs, including patient costs | 56 | — | — | 934.40 (931.51) | 78 | — | — | 459.37 (1195.93) | 65 | — | — | 1219.44 (1210.19) |

[a] Includes preparation, training, intervention delivery and therapist supervision.
[b] Sum of therapist time (in min) on preparing, delivering and reviewing the sessions; missing therapist time was imputed using mean imputation.
CBA: cognitive behavioural approach; NHS: National Health Service; PEP: personalized exercise programme; UC: usual practice.

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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 the 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 with the respective intervention costs of £459 and £717 per patient. Including intervention costs, the complete resource use data over 52 weeks were 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 eight sessions (60% *vs* 40%). Based on intention-to-treat analysis, the average time spent on each session by therapists was longer in the CBA than in the PEP group, resulting in higher total average therapy delivery time per participant for the CBA group (483 min *vs* 324 min) (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 summarized in Table 2. At baseline, there was a small, non-significant difference in unadjusted SF-6D and ICECAP scores in favour of the 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 minimization 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, £665); CBA £845 (95% CI: £717, £993)] and, in the case of PEP, significantly more effective [adjusted mean QALY difference: PEP 0.043 (95% CI: 0.019, 0.068); CBA 0.001 (95% CI: −0.022, 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 (Fig. 1).

The imputed dataset yielded lower mean costs and mean QALYs across all groups, and 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, £511) but a non-significant higher QALY gain of 0.016 (95% CI: −0.003, 0.035), leading to an ICER of £26 822. For CBA, the adjusted QALY difference of 0.006 was in favour of UC, and 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 (Fig. 1). Cost-effectiveness scatterplots are available in Supplementary Fig. S1 (available at *Rheumatology* online).

**Table 2.** Unadjusted mean quality of life score per participant over 52 weeks' follow-up

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

CBA: cognitive behavioural approach; ICECAP-A: ICEpop CAPability measure for Adults; PEP: personalized exercise programme; QALY: quality-adjusted life year; SF-6D: Short Form–Six Dimension; UC: usual practice.

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**Table 3.** Adjusted[a] mean incremental costs, incremental QALYs, and incremental cost-effectiveness ratio over 52 weeks between groups

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

[a] Adjusted for baseline differences (age, gender, baseline Chalder Fatigue Scale score, HADS depression subscale >10 at baseline, baseline utility score, baseline cost and centre).
[b] Bootstrapped non-parametric 95% CI (2.5th, 97.5th centile). Generalized linear model with Gaussian distribution and power 0.25 link function to estimate incremental costs and generalized linear model with Poisson distribution and identity link function to estimate incremental QALYs.
[c] Compared with usual care.
[d] ICER expressed relative to next less costly, non-dominated alternative.
[e] 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.
[f] Imputed dataset ($m = 60$).
CBA: cognitive behavioural approach; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; PEP, personalized exercise programme; QALY, quality-adjusted life year; UC, usual practice.

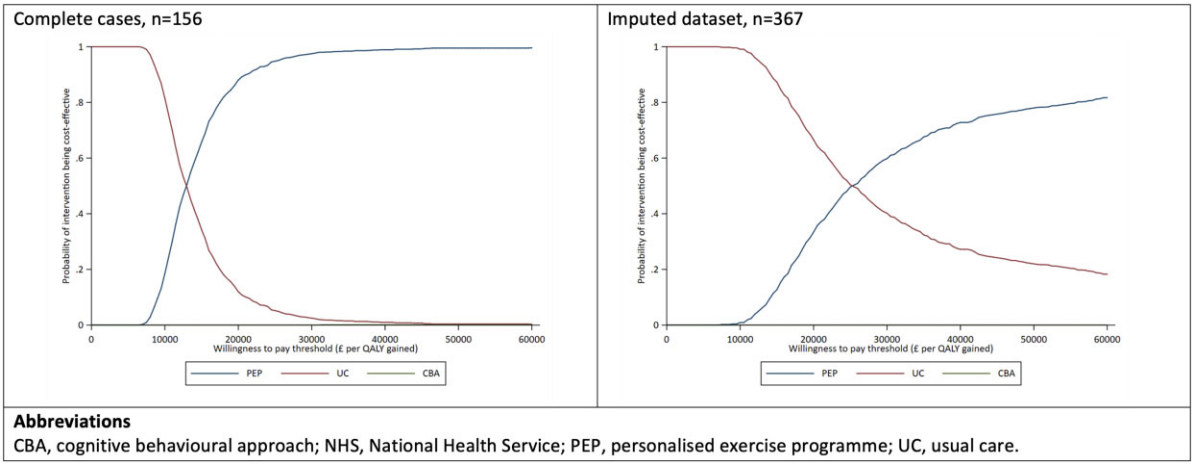


**Figure 1.** Cost-effectiveness acceptability curves of base case analysis (NHS perspective). CBA: cognitive behavioural approach; NHS: National Health Service; PEP: personalized exercise programme; QALY: quality-adjusted life year; UC: usual practice

## 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 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 Fig. S2, available at *Rheumatology* online).

Supplementary Table S4A (available at *Rheumatology* online) demonstrates that none of the minimization 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 fewer 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, while a larger association was seen for the UC group.

## Discussion

This economic evaluation builds on our earlier published results from the LIFT trial that 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

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**Table 4.** Sensitivity analysis of incremental cost-effectiveness ratio over 52 weeks between groups using multiple imputation approach[a]

| Analysis | Costs, mean (95% CI), £[a] | QALYs, mean (95% CI)[a] | Incremental costs, mean (95% CI), £[b,c] | Incremental QALYs, mean (95% CI)[b,c] | ICER, £/QALY[d] |
|---|---|---|---|---|---|
| Using intervention cost when the programme reaches a steady state, $n = 367$ (NHS perspective)[e,f] | | | | | |
| UC | 119.67 (52.74, 209.38) | 0.601 (0.587, 0.616) | | | |
| PEP | 457.15 (392.22, 505.64) | 0.617 (0.599, 0.636) | 337.47 (234.35, 419.91) | 0.016 (−0.003, 0.035) | 21 129 |
| CBA | 773.99 (697.98, 846.27) | 0.595 (0.578, 0.612) | 654.32 (538.45, 756.10) | −0.006 (−0.024, 0.013) | Dominated |
| Including patient costs, $n = 367$ (NHS perspective)[e,g] | | | | | |
| UC | 304.96 (198.83, 416.06) | 0.602 (0.588, 0.617) | | | |
| PEP | 786.90 (667.34, 921.96) | 0.616 (0.597, 0.635) | 481.94 (346.64, 617.33) | 0.014 (−0.006, 0.033) | 35 424 |
| CBA | 1103.95 (950.45, 1250.58) | 0.596 (0.579, 0.613) | 798.88 (661.75, 932.95) | −0.006 (−0.023, 0.012) | Dominated |
| Using ICECAP-A utility score, $n = 367$ (NHS perspective)[e] | | | | | |
| UC | 121.91 (54.10, 221.56) | 0.756 (0.729, 0.782) | | | |
| PEP | 558.48 (495.84, 604.66) | 0.776 (0.748, 0.803) | 436.57 (330.21, 521.89) | 0.019 (−0.011, 0.055) | 22 915 |
| CBA | 847.40 (773.13, 918.20) | 0.750 (0.725, 0.775) | 725.49 (608.37, 825.11) | −0.006 (−0.034, 0.025) | Dominated |
| Including compliant participants, $n = 287$ (NHS perspective)[e,h] | | | | | |
| UC | 118.92 (54.41, 208.22) | 0.603 (0.588, 0.618) | | | |
| PEP | 702.55 (648.29, 755.44) | 0.635 (0.616, 0.656) | 583.63 (470.77, 667.64) | 0.032 (0.013, 0.054) | 17 994 |
| CBA | 985.45 (933.48, 1052.49) | 0.605 (0.589, 0.618) | 866.52 (769.14, 960.42) | 0.002 (−0.017, 0.019) | Dominated |

[a] Adjusted for baseline differences (age, gender, baseline Chalder Fatigue Scale score, HADS depression subscale >10 at baseline, baseline utility score, baseline cost and centre).
[b] Bootstrapped non-parametric 95% CI (2.5th, 97.5th centile). Generalized linear model with Gaussian distribution and power 0.25 link function to estimate incremental costs and generalized linear model with Poisson distribution and identity link function to estimate incremental QALYs.
[c] Compared with usual care.
[d] ICER expressed relative to next less costly, non-dominated alternative.
[e] Imputed dataset ($m = 60$).
[f] Lower intervention costs were applied—PEP £368, CBA £647.
[g] Generalized linear model with Poisson distribution and power 0.5 link function to estimate incremental costs and generalized linear model with Gamma distribution and identity link function to estimate incremental QALYs.
[h] 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 ($n = 90$).
CBA: cognitive behavioural approach; ICECAP-A: ICEpop CAPability measure for Adults; ICER: incremental cost-effectiveness ratio; NHS: National Health Service; PEP: personalized exercise programme; QALY: quality-adjusted life year; UC: usual practice.

interventions, there was a marked difference in costs and QALYs between the two 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, while 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 analysis 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, while 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 while 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 and 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, £1258)] and a non-significant QALY difference [QALY gain per patient of 0.008 (95% CI: −0.008, 0.023)]. The probability that the RAFT programme was cost-effective relative to UC ranged between 28% and 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 of 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

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order to minimize levels of missing data and improve participant retention. Second, future studies might wish to consider stratification based on patient preference, as randomization 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 valued life activities, and reduced levels of work disability and depression [19], but the quality of life measure used in the economic evaluation might fall short in capturing these values.

A strength of this evaluation is the multicentre nature of the study design. The interventions were implemented in six centres throughout the UK. Therefore, the economic analysis should be reasonably generalizable 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 among 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.

## Supplementary material

Supplementary material is available at *Rheumatology* online.

## Data availability

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

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## References

1. Repping-Wuts H, van Riel P, van Achterberg T. Fatigue in patients with rheumatoid arthritis: what is known and what is needed. Rheumatology 2009;48:207–9.
2. Suurmeijer TP, Waltz M, Moum T *et al.* Quality of life profiles in the first years of rheumatoid arthritis: results from the EURIDISS longitudinal study. Arthritis Care Res 2001;45:111–21.
3. Rupp I, Boshuizen HC, Jacobi CE, Dinant HJ, van den Bos GA. Impact of fatigue on health-related quality of life in rheumatoid arthritis. Arthritis Care Res 2004;51:578–85.
4. Gignac MA, Sutton D, Badley EM. Reexamining the arthritis-employment interface: perceptions of arthritis-work spillover among employed adults. Arthritis Care Res 2006;55:233–40.
5. De Croon EM, Sluiter JK, Nijssen TF *et al.* Work ability of Dutch employees with rheumatoid arthritis. Scand J Rheumatol 2005;34:277–83.
6. Aissaoui N, Rostom S, Hakkou J *et al.* Fatigue in patients with ankylosing spondylitis: prevalence and relationships with disease-specific variables, psychological status, and sleep disturbance. Rheumatol Int 2012;32:2117–24.
7. Zonana-Nacach A, Roseman JM, McGwin G *et al.* Systemic lupus erythematosus in three ethnic groups. VI: factors associated with fatigue within 5 years of criteria diagnosis. Lupus 2000;9:101–9.
8. Wang B, Gladman DD, Urowitz MB. Fatigue in lupus is not correlated with disease activity. J Rheumatol 1998;25:892–5.
9. Turan Y, Duruöz MT, Bal S *et al.* Assessment of fatigue in patients with ankylosing spondylitis. Rheumatol Int 2007;27:847–52.
10. Mau W, Listing J, Huscher D, Zeidler H, Zink A. Employment across chronic inflammatory rheumatic diseases and comparison with the general population. J Rheumatol 2005;32:721–8.
11. Hewlett S, Cockshott Z, Byron M *et al.* Patients' perceptions of fatigue in rheumatoid arthritis: overwhelming, uncontrollable, ignored. Arthritis Care Res 2005;53:697–702.
12. Davies H, Brophy S, Dennis M *et al.* Patient perspectives of managing fatigue in Ankylosing Spondylitis, and views on potential interventions: a qualitative study. BMC Musculoskelet Disord 2013;14:163.
13. Deighton C, O'Mahony R, Tosh J, Turner C, Rudolf M; Guideline Development Group. Management of rheumatoid arthritis: summary of NICE guidance. BMJ 2009;338:b702.
14. Tench CM, McCarthy J, McCurdie I, White PD, D'Cruz DP. Fatigue in systemic lupus erythematosus: a randomized controlled trial of exercise. Rheumatology 2003;42:1050–4.
15. Cramp F, Hewlett S, Almeida C *et al.*; Cochrane Musculoskeletal Group. Non-pharmacological interventions for fatigue in rheumatoid arthritis. Cochrane Database Syst Rev 2013:CD008322.
16. Hewlett S, Ambler N, Almeida C *et al.* Self-management of fatigue in rheumatoid arthritis: a randomised controlled trial of

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group cognitive-behavioural therapy. Ann Rheum Dis 2011;70:1060–7.
17. Cramp F. The role of non-pharmacological interventions in the management of rheumatoid-arthritis-related fatigue. Rheumatology 2019;58:v22–8.
18. Hewlett S, Almeida C, Ambler N *et al.* Group cognitive-behavioural programme to reduce the impact of rheumatoid arthritis fatigue: the RAFT RCT with economic and qualitative evaluations. Health Technol Assess 2019;23:1–130.
19. Bachmair EM, Martin K, Aucott L. Remotely delivered cognitive behavioural and personalised exercise interventions for fatigue severity and impact in inflammatory rheumatic diseases: a multicentre randomised controlled parallel open-label group trial (LIFT). Lancet Rheumatol 2022;4:e534–45.
20. Martin KR, Bachmair EM, Aucott L *et al.* Protocol for a multicentre randomised controlled parallel-group trial to compare the effectiveness of remotely delivered cognitive-behavioural and graded exercise interventions with usual care alone to lessen the impact of fatigue in inflammatory rheumatic diseases (LIFT). BMJ Open 2019;9:e026793.
21. Curtis L, Burns A, eds. Unit costs of health and social care 2020. University of Kent Personal Social Services Research Unit, 2020. https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2020 (8 April 2021, date last accessed).
22. Department of Health and Social Care. NHS reference costs 2018/19. Updated 2020. https://www.england.nhs.uk/national-cost-collection/#ncc1819 (15 February 2021, date last accessed).
23. Office for National Statistics. Annual survey of hours and earnings. 2019 provisional. www.ons.gov.uk/employmentandlabourmarket/peopleinwork/earningsandworkinghours/datasets/agegroupashetable6 (24 February 2021, date last accessed).
24. Office for National Statistics. Unpaid work calculator. Annual survey of hours and earnings. 2016. www.ons.gov.uk/visualisations/dvc376/index.html (24 February 2021, date last accessed).
25. Department for Transport. Transport analysis guidance (TAG) data book. www.gov.uk/government/publications/tag-data-book (24 February 2021, date last accessed).
26. Brazier JE, Roberts J. The estimation of a preference-based measure of health from the SF-12. Med Care 2004;42:851–9.
27. Flynn TN, Huynh E, Peters TJ *et al.* Scoring the icecap – a capability instrument. Estimation of a UK general population tariff. Health Econ 2015;24:258–69.
28. Glick HA, Doshi JA, Sonnad SS, Polsky D. Economic evaluation in clinical trials. Handbooks in health economic evaluation. Oxford: Oxford University Press, 2007.
29. Brand J, van Buuren S, le Cessie S, van den Hout W. Combining multiple imputation and bootstrap in the analysis of cost-effectiveness trial data. Stat Med 2019;38:210–20.
30. van Wissen MA, Teuwen MM, van den Ende CH *et al.* Effectiveness and cost-effectiveness of longstanding exercise therapy versus usual care in patients with axial spondyloarthritis or rheumatoid arthritis and severe limitations: the protocols of two parallel randomized controlled trials. Physio Res Int 2022;27:e1933.
31. Guillon M, Rochaix L, Dupont JC. Cost-effectiveness of interventions based on physical activity in the treatment of chronic conditions: a systematic literature review. Int J Tech Assess Health Care 2018;34:481–97.
32. Wasmann KA, Wijsman P, van Dieren S, Bemelman W, Buskens C. Partially randomised patient preference trials as an alternative design to randomised controlled trials: systematic review and meta-analyses. BMJ Open 2019;9:e031151.

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