
Article:
Davis, S. orcid.org/0000-0002-6609-4287, Mon-Yee, M. orcid.org/0009-0001-6921-7529, Sutton, A. orcid.org/0000-0003-2449-2516 et al. (3 more authors) (2025) Cost effectiveness of non-pharmacological interventions for fatigue in patients with long-term conditions: a systematic literature review. Expert Review of Pharmacoeconomics & Outcomes Research. 14737167.2025.2537194. ISSN: 1473-7167

https://doi.org/10.1080/14737167.2025.2537194

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Expert Review of Pharmacoeconomics & Outcomes Research

ISSN: 1473-7167 (Print) 1744-8379 (Online) Journal homepage: www.tandfonline.com/journals/ierp20

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To cite this article: Sarah Davis, Mon Mon-Yee, Anthea Sutton, Joanna Leaviss, Jessica E. Forsyth & Christopher Burton (03 Aug 2025): Cost effectiveness of non-pharmacological interventions for fatigue in patients with long-term conditions: a systematic literature review, Expert Review of Pharmacoeconomics & Outcomes Research, DOI: 10.1080/14737167.2025.2537194

To link to this article: https://doi.org/10.1080/14737167.2025.2537194

EXPERT REVIEW OF PHARMACOECONOMICS & OUTCOMES RESEARCH
https://doi.org/10.1080/14737167.2025.2537194

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SYSTEMATIC REVIEW

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Cost effectiveness of non-pharmacological interventions for fatigue in patients with long-term conditions: a systematic literature review

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ABSTRACT

Introduction: We aimed to assess the cost-effectiveness of non-pharmacological interventions for fatigue in patients with chronic conditions in the UK.

Methods: This systematic review of cost-effectiveness studies aligns with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 statement. Data sources: Electronic databases and citation searches. Inclusion criteria: Studies including adults with one or more long-term health condition, either physical or mental. Exclusion criteria: Studies associated with cancer, long-COVID, post-viral fatigue, medically unexplained conditions, developmental disorders and injuries. Assessment: A single reviewer completed a two-stage sifting process.

Results: Four studies met the inclusion criteria. They included patients with either multiple sclerosis or inflammatory rheumatic conditions, and assessed either cognitive behavioral therapy (CBT) or a personalized exercise program (PEP). CBT was either dominated by usual care or had an incremental cost-effectiveness ratio (ICER) over £30,000. PEP dominated CBT, with the ICER for PEP versus usual care ranging from £13,159 to £35,424.

Conclusions: The economic literature on this topic is much more limited than the clinical effectiveness literature, both in terms of interventions and populations covered. Future research should focus on a de novo economic evaluation to identify interventions with a high potential to be cost-effective across multiple conditions.

Registration: PROSPERO (CRD42023440141)

ARTICLE HISTORY
Received 16 April 2025
Accepted 17 July 2025

KEYWORDS
Chronic conditions; cost-effectiveness; fatigue; non-pharmacological interventions; United Kingdom

1. Introduction

Persistent fatigue is often experienced by people living with long-term medical conditions and it can persist even when the disease has been brought under control using pharmacological interventions [1]. In addition to simple tiredness, fatigue can be marked by a compelling need to rest or difficulty in initiating or maintaining voluntary activities [2,3]. People with fatigue often describe it as far worse than typical tiredness, with significant impacts on their lives [4,5]. Due to its invisible nature, fatigue is frequently overlooked or underestimated by medical professionals [6]. Long-term medical conditions include those that are not currently curable but can be controlled by medication and therapies. Many different non-pharmacological interventions to manage fatigue have been tested in randomized controlled trials (RCTs) in a variety of long-term conditions [7]. These include, but are not limited to, interventions focusing on physical activity (such as increasing or regulating activity levels), psychological therapies, and mind-body approaches like yoga and tai chi. Existing systematic reviews examining the clinical effectiveness of non-pharmacological interventions for fatigue in patients with long-term conditions often mention the need for further research to establish the cost-effectiveness of these interventions [7–10]. Whilst there are published systematic reviews examining the cost-effectiveness of non-pharmacological interventions for patients with chronic fatigue syndrome/myalgic encephalomyelitis [11], and other medically unexplained symptoms [12,13], these populations are distinct from patients whose fatigue is secondary to a chronic condition.

This review aimed to assess the cost-effectiveness of non-pharmacological interventions for fatigue in patients with chronic conditions in a UK healthcare setting based on published literature.

2. Methods

2.1. Review design, protocol and registration

This work was part of a broader review of the evidence examining both clinical and cost-effectiveness and the protocol covering both the clinical and cost-effectiveness reviews was registered with PROSPERO (CRD42023440141). This paper reports the systematic review of cost-effectiveness studies, conducted alongside a separate review of clinical effectiveness and network meta-analysis reported elsewhere. As we anticipated the studies to cover a range of interventions and population pairings, which would be

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/14737167.2025.2537194

Article highlights

- While several RCTs have assessed the clinical effectiveness of non-pharmacological interventions for fatigue in long-term medical conditions, no systematic review has examined the cost-effectiveness of such interventions for fatigue secondary to these conditions.
- Studies involving patients with inflammatory rheumatic conditions or multiple sclerosis suggested that the difference in quality-adjusted life-years (QALYs) between non-pharmacological interventions and usual care was small and generally statistically insignificant.
- Future research should focus on a *de novo* economic evaluation using clinical effectiveness data across different chronic conditions to identify interventions with the greatest potential for cost-effectiveness.

likely to preclude any formal synthesis of findings, we planned to use a narrative approach to summarize cost-effectiveness findings.

2.2. Literature search

The databases searched included Ovid MEDLINE(R), Embase, CINAHL, APA PsycInfo (via Ovid), Web of Science (Science Citation Index, Social Sciences Citation Index and Science and Social Sciences Conference proceedings), National Health Service (NHS) Economic Evaluations Database, EconLit (via Ovid) and TUFTs Cost-Effectiveness Analysis (CEA) Registry. Databases were searched up to 3 April 2024 using search strategies that combined population terms for long-term conditions, terms for fatigue and a methodological search filter to identify cost-effectiveness studies. Subject headings (where available) were combined with free-text terms using Boolean operators (see Appendix 1 in the electronic supplementary material [ESM]). Searches were restricted to English language articles published from 1990. Grey literature was not searched beyond that which would be identified from the bibliographic databases, e.g. conference abstracts, dissertations, and reports.

2.3. Study selection

A two-stage sifting process, examining title and abstracts first, followed by full text papers was employed by a single reviewer (SD). Published systematic reviews were excluded but reference lists were searched for eligible studies. The inclusion/exclusion criteria for populations and interventions were in-line with those specified in the review of clinical effectiveness studies [14]. The following study eligibility criteria were structured using the PICOS framework.

2.3.1. Population

We included studies in adults with one or more long-term health conditions which could be either physical or mental. We excluded studies in patients with cancer, long-COVID, post-viral fatigue, medically not yet explained conditions, developmental disorders and acute conditions resulting from accidents or injuries.

2.3.2. Interventions

We included studies which compared any non-pharmacological intervention where treating fatigue was the explicit aim of the intervention. This included interventions with multiple components, even where one component is pharmacological. The interventions could be delivered face-to-face or remotely to either groups or individuals. Trial-based economic evaluations were cross-checked against the list of trials included in the clinical effectiveness review as these had already been sifted according to whether the intervention specifically targeted fatigue, meaning that this judgment was not based on a single-reviewer's opinion.

2.3.3. Comparators

Acceptable comparator arms included 'usual care,' attentional control, or other non-pharmacological interventions. We excluded studies that only compared a non-pharmacological intervention to a pharmacological intervention.

2.3.4. Outcomes

In terms of study design and outcomes, we only included full economic evaluations that reported both costs and benefits measured in terms of quality-adjusted life-years (QALYs). These could be either economic evaluations conducted alongside clinical trials or evaluations using a decision-analytic modeling approach.

2.3.5. Settings

We restricted the review to UK NHS settings but included interventions delivered in primary, secondary, tertiary care, or community-based settings. The rationale for this is that resource use and costs are likely to vary between different countries. We included studies reporting costs using either a societal perspective or an NHS and personal social services (PSS) perspective, but reported both when these were presented separately.

2.4. Quality appraisal

The applicability of the study to the research question and its methodological limitations were assessed using the checklist applied in NICE guidelines [15].

3. Results

The search identified 2653 unique records, with 2621 excluded based on either the title or the abstract, leaving 32 records to be examined at full-text (see Figure 1). Of these, 26 records were excluded after considering the full-text article, with the two most common reasons being that the intervention did not meet the inclusion criteria because it did not specifically target fatigue, or that the outcomes did not meet the inclusion criteria because the full-text article did not report both costs and benefits (see Appendix 2 in ESM). In addition, one record was a systematic review, which was excluded after the full-text had been examined to identify any relevant primary studies. No additional studies were identified from this systematic review. Four studies were considered to have met the

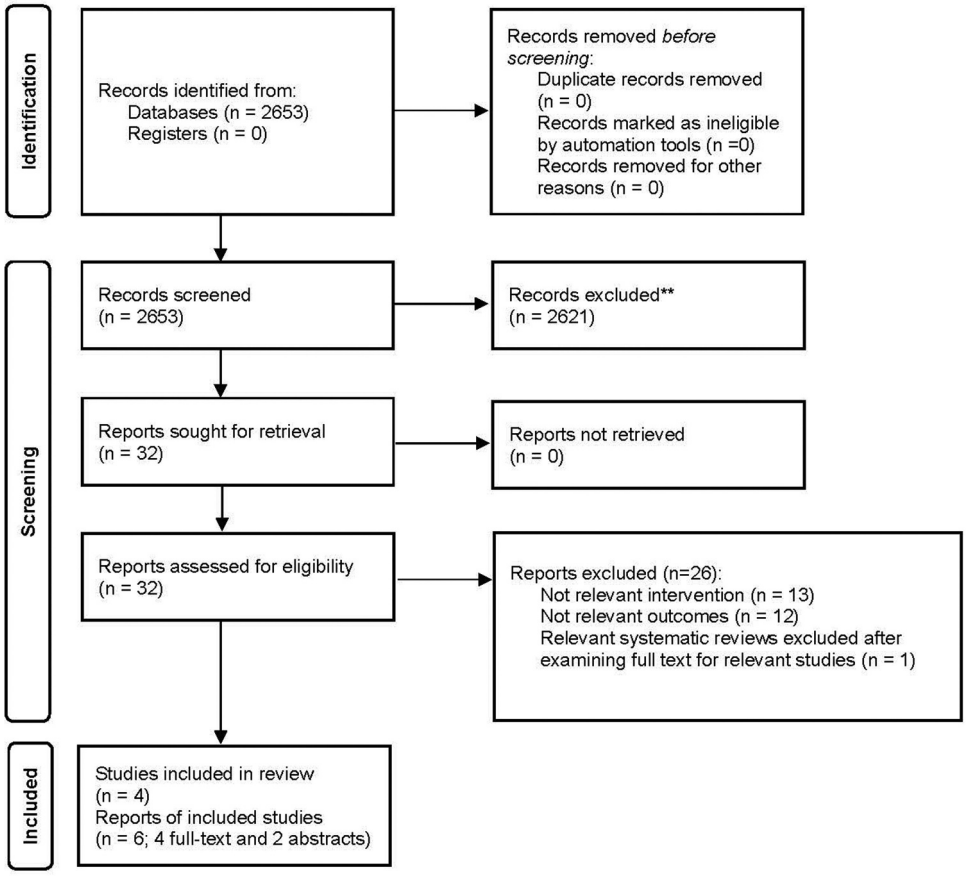

Figure 1. Flow chart for identification of economic evaluations.

inclusion criteria [16–19], with two of these studies being described in both a full text article and an associated conference abstract [20,21].

The main characteristics of the four included studies are summarized in Table 1. All four studies were economic evaluations conducted alongside either a full RCT [16,17,19], or a pilot RCT [18], and none were decision-analytic modeling studies [16–19]. Two studies recruited patients with rheumatoid arthritis or other inflammatory rheumatic conditions (Reducing Arthritis Fatigue by Clinical Teams [RAFT] RCT and Lessening the Impact of Fatigue in Inflammatory Rheumatic Diseases: a Randomized Trial [LIFT] RCT) [16,17], and the remaining two studies recruited patients with multiple sclerosis (Fatigue: Applying Cognitive behavioral and Energy effectiveness Techniques to lifestyle [FACETS] and MS-Invigor8) [18,19]. Both of the studies in patients with inflammatory rheumatic diseases examined interventions described as cognitive behavior therapy (CBT) with one of these studies comparing this to a personalized exercise program (PEP) [16,17]. Both of the studies in patients with multiple sclerosis examined interventions described by the study investigators as fatigue management programs [18,19]. However, both of these programs included cognitive-behavioral approaches and in our related clinical effectiveness review, the two fatigue management programs were categorized as CBT [14]. Two of the interventions were delivered to groups of patients in a face-to-face setting [17,19], whereas both the CBT and PEP programs in the LIFT RCT were delivered by telephone [16], and the MS-Invigor8 program was a web-based intervention with telephone support [18].

All four papers included a comparator arm that was intended to act as a nonintervention control, but this varied between studies. The comparator arm in the RAFT RCT consisted of a brief discussion of a fatigue self-management booklet with a research nurse, and this was described as being representative of usual care [17]. In the LIFT RCT the CBT and PEP intervention arms were provided in addition to usual care and compared against usual care alone [16]. It is stated in the main clinical paper for the LIFT RCT, that as a minimum participants all patients received usual care in the form of established educational materials, with the booklet provided being the same as offered in the RAFT study [22]. In the pilot RCT comparing MS-Invigor8 to control, a waiting list control was employed whereby patients received access to the intervention but at a later time after completion of the study assessments [18]. In the remaining study patients in the control arm received current local practice with the FACETS intervention being offered in addition to current local practice and no attempt was made to standardize or restrict what was offered within current local practice [19]. The comparator arms of these studies were all classified as usual care in our related clinical effectiveness review [14].

In the assessment of applicability, three of the studies were considered to be directly applicable to the review question

Table 1. Summary of included cost-effectiveness studies.

Author, year (trial name)	Long-term condition	Fatigue eligibility criteria	Non-pharmacological interventions	Comparator arms	Study design	Perspective	Applicability and limitations[a]
Moss-Morris 2012 (MS-Invigor8 pilot RCT) [12]	Multiple sclerosis	Score > 4 on the Chalder Fatigue Scale (binary scoring methods)	Web-based cognitive behavioral therapy self-management with telephone support (MS-Invigor8)	Waiting list control (access to MS-Invigor8 without telephone support at 10 weeks)	Preliminary economic evaluation based on within-trial analysis of pilot RCT with time horizon of 10 weeks	NHS and PSS perspective[b] Intervention costs were explicitly excluded.	Partially applicable; potentially serious limitations.
Thomas 2013 (FACETS RCT) [13]	Multiple sclerosis	Fatigue Severity Scale total score > 4.	Group-based fatigue management programme (FACETS) in a face-to-face setting in addition to access to CLP.	CLP	Within-trial economic evaluation with 24-week time-horizon.	NHS and PSS perspective. Private healthcare costs are reported separately.	Directly applicable; minor limitations
Hewlett 2019 (RAFT RCT) [11]	Rheumatoid arthritis	Fatigue severity score of ≥ 6 out of 10, as measured by the Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale (BRAF-NRS)	Group CBT (RAFT) in a face-to-face setting	Usual care (Brief intervention and self-management booklet)	Within-trial economic evaluation with primary analysis at 26 weeks and secondary analysis at 2 years	Societal perspective for main analysis. NHS and PSS perspective reported as scenario analysis	Directly applicable and minor limitations
Chong 2023 (LIFT RCT) [10]	Inflammatory rheumatic disease	Persistent fatigue (> 3 months) that was clinically significant (≥6 on numerical rating 0–10 scale measuring average level of fatigue during the past 7 day) [16]	CBA delivered by telephone + usual care PEP delivered by telephone + usual care	Usual care (education booklet)	Within-trial economic evaluation over 56 weeks	NHS perspective in main analysis. Patient costs included in a scenario analysis.	Directly applicable and minor limitations

RCT: randomized controlled trial, NHS: National Health Services, PSS: Personal Social Services, CLP: current local practice, CBA: cognitive behavioral approach, PEP: personalized exercise programme.
[a]See Appendix 3 in ESM for checklist detailed checklist assessment of applicability and methodological limitations.
[b]The perspective was not specifically stated but the resource use items included would be consistent with an NHS and PSS perspective.

[16,17,19]. The remaining study was considered to be partly applicable because it did not assess intervention costs [18]. This same study, which was a pilot RCT, was considered to have serious limitations because the time horizon was limited to 10 weeks post-intervention [18]. The remaining studies were economic evaluations conducted alongside full RCTs and these were all judged to have minor limitations [16,17,19]. The time horizons employed in the remaining studies ranged from 24 weeks to 2 years [16,17,19], although the study which reported a 2-year horizon used a 26-week horizon in its main analysis [17]. This study applied discounting at 3.5% to both costs and QALYs occurring in the second year [17]. No other studies incorporated discounting but this was not considered to be a significant limitation given the time horizons employed in the remaining studies were 56 weeks or less [16,19].

One study reported results using a societal perspective, which included costs falling on the NHS and PSS, costs falling on the individual patient and productivity costs [17]. However, this study also reported an analysis restricted to an NHS and PSS perspective, albeit only for the shorter time horizon of 26 weeks [17]. One study reported using an NHS perspective in their primary analysis, but explored the impact of including patient costs in a sensitivity analysis [16]. One study described their analysis as taking an NHS and PSS perspective but some included costs which were classed as private healthcare costs [19]. The pilot RCT did not explicitly report its perspective, describing the included costs as 'service costs,' but the items of resource use included suggest the approach taken was consistent with an NHS and PSS perspective [18].

Two studies measured benefits using the EQ-5D [17,18]. One study used SF-6D scores calculated from the SF-12 [16]. One study reported results using both EQ-5D and SF-6D with EQ-5D used in the primary analysis [19]. All four studies reported adjusting for differences in baseline utilities when calculating QALYs.

The cost-effectiveness results presented in the four studies are summarized in Table 2. Although all four studies reported both costs and QALYs, only two reported an incremental cost-effectiveness ratio. The pilot RCT was unable to report this because it did not include intervention costs in its analysis, and it therefore only reported differences in QALYs and differences in costs associated with resource use outside of the intervention [18]. One study did report intervention costs for the FACETS program, but did not combine these with costs associated with other resource use and instead reported these two types of costs separately [19].

All three of the full RCTs reported conducting sensitivity analyses to explore the potential impact of sources of uncertainty, whilst no such analyses were reported for the pilot RCT. Two studies used imputation to account for missing data but also presented complete-case analyses as sensitivity analyses [16,17]. Two studies reported sensitivity analyses that attempted to estimate future intervention costs when interventions are fully rolled-out [16,17]. Two studies presented the uncertainty around the ICER using cost-effectiveness acceptability curves [16,17], whilst a third study used probabilistic sampling to describe the uncertainty around the intervention costs [19]. One study reported a sub-group analysis for compliant patients [16], and another reported a subgroup analysis for patients who still met the fatigue eligibility criteria at baseline [17].

Hewlett et al. concluded that the RAFT CBT program had a low probability of being cost-effective (< 50%) in patients with rheumatoid arthritis when applying the £20,000 to £30,000 threshold usually applied by the UK's National Institute for Health and Care Excellence [17]. The only analysis presented in which the probability of being cost-effective was over 50% was when the analysis was restricted to exclude those whose fatigue scores fell below the eligible range (BRAF-NRS severity ≥ 6) between the screening and baseline measurements. This analysis provided an ICER under £20,000 per QALY, when using results from 26 weeks. However, this analysis was not provided using a 2-year horizon and it is possible that the QALY gain may have narrowed over the longer time frame as was seen in the full analysis set.

Chong et al. found that CBT was dominated by PEP in all of the presented analyses and CBT was dominated by usual care in the analysis using multiple imputation to account for missing data [16]. In this analysis PEP had an ICER of £26,822 and a 23% probability of being cost-effective at a £20,000 per QALY threshold. The ICERs for PEP vs UC ranged from £13,159 when using a complete case approach to £35,424 when using the multiple regression approach but including patient costs. The ICER was £17,994 in the subgroup of patients who were classified as being compliant to the intervention (≥3 sessions attended).

Thomas et al. also found that CBT was dominated by usual care due to there being additional costs associated with delivering the intervention, a non-statistically significant difference in costs associated with other resources use, and a non-significantly significant decrease in QALYs when using either the EQ-5D or the SF-6D to measure utilities over 24 weeks [19].

Moss-Morris et al. did find a small but statistically significant difference in QALYs between the MS-Invigor8 intervention and control over the 10-week period of follow-up [18]. However, it is unclear whether this difference would have persisted if patients had been followed up beyond the duration of the intervention. Costs for resource use not directly attributable to delivering the intervention were found to be similar between the two arms. As this pilot RCT did not measure the intervention costs, it is not possible to say whether the intervention was cost-effective, although the analysis does provide an upper limit of £300 per person for the intervention costs when valuing a QALY at £20,000.

4. Discussion

We believe this to be the first review of cost-effectiveness studies on non-pharmacological interventions for patients with long-term- medical conditions, as no previously published relevant reviews were identified during sifting. We identified only four published economic evaluations addressing the cost-effectiveness of non-pharmacological interventions for fatigue in patients with long-term conditions. All four studies included an intervention that used a cognitive behavioral approach although two of these studies described the

Table 2. Summary of main cost-effectiveness findings.

Author, year	Incremental costs in £ (mean, 95%CI)	Incremental QALYs (mean, 95%CI)	Cost-effectiveness (ICER, £)	Uncertainty
Moss-Morris 2012 (MS-Invigor8 pilot) [18]	NHS + PSS perspective: Incremental costs not reported[a]	Incremental QALYs: 0.015 (SD/95% CI was not reported). (p value = 0.038)	NA.	At the 20K threshold, the cost of intervention should not be more than £300 per person or £50 per session.
Thomas 2013 (FACETS RCT) [19]	NHS + PSS + private:[b] Incremental costs excluding intervention[c]: 50 (−62 to 173) Incremental costs including intervention[c]: 503 NHS perspective:[b] Incremental costs excluding intervention[c]: 36 (−60 to 141) Incremental costs including intervention[c]: 489	EQ-5D estimates: −0.02 (−0.05 to 0.02) SF-6D estimates: −0.00 (−0.01 to 0.01)	FACETs intervention is dominated by UC based on incremental costs and incremental QALYs reported	There was uncertainty around intervention costs and assumptions in cost estimates, e.g. staff input time for FACETS delivery. By using probabilistic sampling of the distribution of staff input time, intervention costs range from £331 to £585 per participant. (Mean cost = £453) By using less experienced/less costly health professionals, cost of intervention = £414 per participant (£311 to £526)
Hewlett 2019 (RAFT RCT) [17]	Societal perspective at 26 weeks: 434 (−389 to 1258) NHS&PSS analysis at 26 weeks: 279 (−393 to 950) Societal perspective at 2 years: 1,012 (−2,318 to 4,341)	At 26 weeks: 0.008 (−0.008 to 0.023) At 2 years: −0.010 (−0.075 to 0.054)	Societal perspective at 26 weeks: 55202 per QALY NHS&PSS perspective at 26 weeks: 34,878 per QALY Societal perspective at 2 years: Control dominates CBT	Societal perspective at 26 weeks: Probability of CE under £20K: 0.28 Probability of CE under £30K: 0.35 NHS&PSS: Probability of ICER under £20K: 0.38 Probability of ICER under £30K: 0.46 Societal perspective at 2 years: Probability of ICER under £20K: 0.26 Probability of ICER under £30K: 0.26 Subgroup with eligible fatigue scores at baseline: 17,214 per QALY; Probability of ICER under £20K: 0.52 Probability of ICER under £30K: 0.60
Chong 2023 (LIFT RCT) [16]	NHS perspective:[e] CBA+UC vs UC: 724 (609 to 826) PEP+UC vs UC: 428 (324 to 511) NHS + patient costs:[e] CBA+UC vs UC: 799 (662 to 933) PEP+UC vs UC: 482 (347 to 617)	NHS perspective:[e] CBA+UC vs UC: −0.006 (−0.024 to 0.013) PEP+UC vs UC: 0.016 (−0.003 to 0.035) NHS + patient costs:[e] CBA+UC vs UC: −0.006 (−0.023 to 0.012) PEP+UC vs UC: 0.014 (−0.006 to 0.033)	NHS perspective:[e] CBA is dominated by both UC and PEP. PEP+UC vs UC: 26,822 NHS + patient costs:[e] CBA is dominated by both UC and PEP. PEP+UC vs UC: ICER = 35,424	NHS perspective:[c] PEP dominates CBA in all scenarios in sensitivity analysis. Probability of ICER under £20K: 0.23 (PEP vs UC) ICER for PEP vs UC in sensitivity analyses: (1) Complete-case analysis; £13,159 per QALY (probability of ICER under £20K: 0.88) (2) Using intervention cost when the program reaches a steady state; £21,129 per QALY (3) Including only compliant participants; £17,994 per QALY (probability of ICER under £20K: 0.50)

CI: confidence interval, NHS: National Health Services, PSS: Personal Social Services, QALY: quality-adjusted life-years, ICER: incremental cost-effectiveness ratio, EQ-5D: EuroQol 5 Dimension, SF-6D: Short Form 6D, UC: usual care, CBT: cognitive behavioral therapy, CBA: cognitive behavioral approach, PEP: personalized exercise program.

[a]Mean costs of resource use: MS-Invigor8: 211(−375 to 797), Control group: 214 (−254 to 682).

[b]The values were estimated by combining the mean intervention cost per attendee and the total NHS plus private resource use costs for 3-month time period using costs adjusted for baseline covariates.

[c]£453 per attendee.

[d]The values were estimated by combining the mean intervention cost per attendee and the total NHS resource use cost for 3-month time period using costs adjusted for baseline covariates.

[e]Multiple imputation used to account for missing data; this means QALYs differ slightly when repeating the analysis including patient costs.

interventions as self-management interventions rather than a CBT program. Only one of the studies included an exercise-based intervention and no other types of non-pharmacological therapies were represented in the included studies. Furthermore, all of the studies recruited either patients with MS or patients with an inflammatory rheumatic illness. The economic literature is therefore not representative of the broader literature on clinical effectiveness in this area which covers a much broader range of interventions and a much broader range of conditions [14].

All four studies found small and generally non-statistically significant difference in QALYs between the non-pharmacological intervention and the control arm. The exceptions were a small pilot RCT which a found small statistically significant difference in QALYs, but this study was considered to have significant limitations due to the short duration of follow-up

[18]. It also used a waiting list control which could have a nocebo effect on patients' quality of life. The other exception was a small and statistically significant gain in QALYs for a personal exercise program versus usual care in patients with inflammatory rheumatic diseases, but a non-statistically significant difference in QALYs was found in this study when multiple imputation was used to account for missing data [16]. In terms of cost-effectiveness outcomes, CBT was either dominated or had an ICER exceeding £30,000 per QALY gained when compared with usual care. CBT was also found to be dominated by PEP. The ICERs for PEP versus usual care ranged from approximately £13,000 to £35,000 per QALY gained.

A limitation of this review was that the sifting process was conducted by a single reviewer. However, this review was conducted alongside a parallel review of clinical effectiveness studies allowing judgments on exclusion based on population or interventions for any trial-based analyses to be cross-checked with the clinical effectiveness review, thereby minimizing the bias of having a single reviewer. The small number of studies identified and the heterogeneity in the populations and interventions addressed in those studies meant we were unable to conduct a quantitative synthesis of the findings or an assessment of publication bias.

5. Conclusion

Overall, we therefore conclude that there is a lack of strong evidence to support the cost-effectiveness of non-pharmacological interventions to reduce fatigue in patients with long-term conditions in the published literature, when applying the threshold for cost-effectiveness usually applied in a UK context (£20,000 to £30,000 per QALY).

6. Expert opinion

Fatigue in long term conditions is common and is a major driver of poor quality of life. Clinical effectiveness studies suggest that non-pharmacological interventions can improve outcomes in patients with long term conditions providing they possess certain characteristics. Our patient and public involvement work suggests that these would be acceptable across a wide range of conditions. The cost-effectiveness evidence currently available is restricted to a small number of within-trial economic evaluations which examined a limited number of interventions in a narrow range of conditions. In addition, most RCTs recruit patients with either a diagnosis of a specific condition, such as the FACETS RCT which recruited patients with multiple sclerosis, or patients whose diagnosis falls within a group of similar conditions, such as the LIFT RCT who recruited patients with inflammatory rheumatic conditions. This means that trial-based assessments of cost-effectiveness are also usually limited to a specific condition or a group of similar conditions. However, the experience of fatigue is common across many long-term conditions and the response of patients to interventions which specifically aim to reduce fatigue associated with the long-term condition, rather than treat the underlying condition, may be similar across different conditions. We would argue that evaluating the cost-effectiveness of fatigue interventions across patients with a diverse range of conditions using a transdiagnostic approach, would be the appropriate next step to take research in this area forward. We propose that a *de novo* analysis, using decision-analytic modeling methods, should be undertaken to determine which non-pharmacological fatigue interventions have the potential to be cost-effective across a broad range of long-term conditions. Such an analysis would require an evaluation of clinical effectiveness from a systematic review of RCTs encompassing a broad range of interventions and conditions. As it is common for RCTs of fatigue interventions to report fatigue outcomes rather than direct measures of health utility, it may be necessary to use a mapping algorithm to estimate health utilities from the fatigue measures commonly reported. Whilst this would introduce some additional uncertainty in the QALY estimates, we believe this would be offset by the benefit of being able to estimate clinical effectiveness from a broader range of studies. The estimate of clinical benefits, driven by changes in fatigue, but expressed as QALYs, could then be combined with estimates of intervention costs for different categories of non-pharmacological interventions, to identify those which have the potential to be cost-effective. The findings from this *de novo* analysis could then be used to inform the design of future pragmatic RCTs in patients with a diverse range of long-term conditions, to more accurately estimate the cost-effectiveness for those fatigue interventions which have demonstrated the potential to be cost-effectiveness within the decision analytic modeling.

Funding

This work was funded by the National Institute for Health and Care Research (NIHR) with the grant number [NIHR154660].

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Author contributions

S Davis reviewed studies, extracted and analyzed the data from the review. S Davis and M Mon-Yee analyzed the data and wrote the manuscript. A Sutton undertook searches and contributed to the manuscript. All authors contributed to development, analysis, writing and editing the manuscript. All authors read and approved the final version.

Acknowledgments

The authors would like to thank Helen Dawes, Vincent Deary, Julia Newton, Kate Fryer, Samantha McCormick, David Coyle and Shijie Ren who contributed to the design of the research and specification of the review protocol.

Data availability statement

Full data extracted from each of the studies is available in the electronic supplementary material.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

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