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Synopsis

# Effectiveness of non-pharmacological interventions for fatigue in adults with long-term conditions: a synopsis of the EIFFEL mixed-methods evidence synthesis

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## Abstract

**Background:** Fatigue is common in many long-term medical conditions. Interventions to date have largely been in single conditions.

**Objective:** To conduct a mixed-methods evidence synthesis of the clinical and cost-effectiveness and acceptability of non-pharmacological interventions for fatigue in adults with long-term medical conditions.

**Methods:**

**Eligibility criteria:** Randomised controlled trials, cost-effectiveness studies, or qualitative studies of non-pharmacological interventions for fatigue in long-term medical conditions where fatigue was either a criterion for inclusion, the primary target of the intervention, or the primary or coprimary outcome. Studies of post-infectious, post-traumatic, cancer-related or idiopathic fatigue were excluded.

**Information sources:** Searches used the MEDical Literature Analysis and Retrieval System, Excerpta Medica dataBASE, Cumulative Index to Nursing and Allied Health Literature, and American Psychological Association PsycInfo® (American Psychological Association, Washington, DC, USA) databases. We used systematic CLUSTER searching for qualitative studies and Epistemonikos for systematic reviews.

**Involvement of patients:** We held three rounds of five focus groups involving people with fatigue in long-term conditions to ensure that assumptions in, and reporting of, the research had validity with the patient population.

**Risk of bias:** Risk-of-bias assessment of all studies included in the network meta-analysis was undertaken using an adapted version 2 of the Cochrane risk-of-bias tool for randomised controlled trials.

**Synthesis of results:** Clinical effectiveness evaluation used random effects network meta-analyses at three time points. The cost-effectiveness analysis involved a de novo analysis of interventions identified as clinically effective. The qualitative synthesis involved a thematic synthesis of primary studies of interventions and a mega-synthesis of reviews of patient experience of fatigue across different conditions. Focus groups were analysed by thematic analysis, and findings from all work packages were integrated in a final synthesis by the research team.

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**Results:**
**Included studies:** The clinical effectiveness review included 88 randomised controlled trials, involving 27 interventions, with 6636 participants included at end of treatment, 1849 in the short term and 2322 in the long term.
**Synthesis of results:** Compared to usual care at long-term follow-up, cognitive–behavioural therapy-based interventions and physical activity promotion showed statistically significant reductions in fatigue (standardised mean difference −0.4, 95% credible interval −0.63 to −0.21, 9 studies; and −0.52, −0.86 to −0.18, 2 studies), respectively. Effective interventions provided positive net monetary benefit versus usual care, particularly when delivered in a group format, when valuing a quality-adjusted life-year at £20,000. Individuals vary in their experience of fatigue in ways that are not simply due to their medical condition, indicating that interventions need to be adaptable to individuals' experiences and capabilities.
**Discussion:** The evidence base is relatively small, heterogeneous and includes studies at moderate to high risk of bias. More than half of the included trials were in multiple sclerosis.
**Interpretation:** Interventions for fatigue that support people to increase physical activity or are based on cognitive–behavioural therapy are acceptable and effective in reducing fatigue in people with different long-term medical conditions, with the potential to be cost-effective. Based on the qualitative synthesis, we propose a three-stage component model for interventions.
**Future work:** Future trials should focus on the feasibility and effectiveness of transdiagnostic fatigue services, fatigue interventions in multimorbidity, and investigations of emerging non-invasive stimulation interventions.
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## Introduction



### *Rationale for research and background*

Persistent fatigue is common in long-term medical conditions, particularly when multiple conditions are present.[2] Alongside tiredness, it includes a sense of needing to rest, or of difficulty in initiating or sustaining voluntary effort.[3,4] People with medical conditions describe their fatigue as 'more than ordinary tiredness'[5] with impacts that go beyond the symptom itself.[6,7] In addition to wanting their fatigue reduced, and a return to meaningful activities,[8] people want their experience of fatigue to be validated.[9] However, many patients report feeling that others, including clinicians, do not take fatigue seriously.[10]

While fatigue is common in medical conditions, its presence correlates poorly with disease severity,[11–14] and it often persists after the disease has been brought under control.[15] Commentators have suggested that fatigue appears to be a transdiagnostic phenomenon with similarities in experience and impairment across different conditions.[10] Current models of fatigue include biological[16] and psychosocial factors,[2,12] with increasing interest in the role of altered signalling between the brain and body.[17–20] There are currently no licensed drug treatments for fatigue in long-term conditions.

A diverse range of non-pharmacological interventions have been developed to overcome fatigue in medical conditions. These include interventions focusing on physical activity (either managing or increasing activity), psychological therapies and body–mind interventions (such as yoga). In practice, many fatigue rehabilitation and self-management (SM) programmes contain multiple components. To patients, such programmes may pose challenges to acceptability: for instance, appearing illogical (physical exercise when they are already exhausted) or stigmatising (psychological interventions implying fatigue can be overcome just by thinking differently). These conceptual barriers to engagement with interventions persist as an important aspect of this problem.[21]

This study was conducted in response to a commissioned call from the National Institute for Health and Care Research (NIHR) to evaluate the effectiveness and cost-effectiveness of interventions for fatigue in long-term conditions.

### *Aim and objectives*

The overall aim of this work was to answer the research question 'What is the effectiveness, cost-effectiveness and acceptability of non-pharmacological interventions and strategies to manage fatigue in people with long-term medical conditions?'

The objectives were to

1. Conduct a quantitative evidence synthesis focusing on effectiveness, cost-effectiveness and acceptability.
2. Conduct a qualitative evidence synthesis (QES) examining acceptability.
3. Integrate evidence from the quantitative and qualitative reviews to provide accessible and clear syntheses of our findings.
4. Produce recommendations for further research.
5. Work with patients throughout the study to ensure that our methods, interpretation and recommendations make sense and meet the needs and priorities of people experiencing fatigue in long-term conditions.

## *Methods*

The study comprised four work packages (WPs): (1) a systematic review and quantitative synthesis of clinical effectiveness, (2) a cost-effectiveness analysis (CEA), (3) a QES which comprised two separate reviews and (4) a qualitative focus group study of people with lived experience. The two qualitative evidence syntheses addressed patients' experience of interventions for fatigue (primary studies), in order to address questions of acceptability, and of patients' more general experience of fatigue in long-term conditions (review-level evidence).

The WPs were linked as follows: the systematic review of clinical effectiveness was core, but decisions about its conduct/analysis were informed by the focus groups to ensure that the assumptions we used had validity with patients. The CEA focused on interventions which met criteria of effectiveness based on statistical significance in the clinical effectiveness synthesis. The first QES (of intervention acceptability) focused on behavioural interventions included in the clinical effectiveness study. The second synthesis (focusing on similarities in the experience of fatigue) across long-term conditions not only helped target the review of interventions but also acted as triangulation for the focus groups. We took the view that this was particularly important in the light of the emerging conclusion that there were similarities being observed across conditions, which may offer justification to support a transdiagnostic approach to clinical management. We made the decisions to extend the QES with the second review and to formally analyse the focus group study (rather than simply use it to inform the other analyses) during the study.

Reports of the quantitative synthesis, CEA and QES of patients' experience of intervention form the set of core research papers agreed in our publication. Further publications beyond this plan are in progress, examining similarities and differences in patient experience (focus groups and QES) across conditions.

### Quantitative synthesis of clinical effectiveness

This systematic review was conducted and reported in accordance with the Cochrane Handbook[22] and Preferred Reporting Items for Systematic review and Meta-Analysis guidelines.[23] The inclusion and exclusion criteria were defined using the Population, Intervention, Comparison, Outcomes and Setting framework. The protocol for this review was registered with the CRD PROSPERO database CRD42023440141. We amended the review after the protocol was published to limit the analysis to countries with comparable healthcare systems to the UK.

Population: adults with any long-term condition, using the NHS definition as 'an illness that cannot be cured but that can usually be controlled with medicines or other treatments'. The commissioning brief specifically excluded fatigue in people with cancer, in relation to or following from infection [human immunodeficiency virus, hepatitis C, long COVID and myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS)] or resulting from injuries or developmental disorders. It also excluded conditions in which symptoms (rather than observable pathology) were the defining features rather than observable pathology (e.g. fibromyalgia or irritable bowel syndrome).

Interventions: any non-pharmacological intervention in which a stated explicit aim or primary outcome was to address fatigue. We excluded interventions that were specific to a condition (e.g. pulmonary rehabilitation in lung disease) or to a problem other than fatigue (e.g. vestibular rehabilitation for balance problems). There was no restriction on how interventions were delivered.

Comparators: 'usual care' (UC), waiting list control, sham or placebo (for external stimulation or nutritional interventions), another non-pharmacological intervention or attentional control.

Outcomes: an established measure for fatigue at one of three time points for follow-up: end of treatment, short term (up to 3 months after end of treatment) and long term (any time point thereafter).

Setting: interventions which could be delivered in an outpatient or community-based setting. We excluded studies set in countries with healthcare systems that are not comparable to the UK.

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### *Information sources*

A comprehensive search of bibliographic databases to identify randomised controlled trials (RCTs) was conducted in September–October 2023 and updated in September 2024. All searches were performed on the following databases: Ovid MEDical Literature Analysis and Retrieval System (MEDLINE), Excerpta Medica dataBASE (EMBASE) (via Ovid), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (via EBSCO), American Psychological Association (APA) PsycInfo® (American Psychological Association, Washington, DC, USA) (via Ovid), Web of Science Core Collection (Science Citation Index and Social Sciences Citation Index), Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews.

### *Study selection and data collection*

We carried out a two-stage sifting process for inclusion of studies (title/abstract, then full-paper sift), using Covidence (Melbourne, VIC, Australia) to manage the selection process. We extracted the following data: population and study characteristics (and numbers), intervention characteristics, follow-up (time and attrition) and results.

### *Risk-of-bias assessment of included studies*

We assessed risk of bias of included studies using a version of the Cochrane risk-of-bias tool (RoB2) for RCTs[24] adapted for handling the large number of included studies. For this, we used a shortened version of the Cochrane RoB2 tool[24] (with 15, rather than 22, 'signalling questions').

### *Classification of conditions and interventions*

We categorised conditions and interventions in order to pool evidence from similar interventions and avoid the generation of sparse or disconnected networks within the network analysis. Conditions were grouped into broad categories (e.g. musculoskeletal conditions) except where a large number of studies were in one condition [e.g. multiple sclerosis (MS)].

We employed an iterative inductive approach to intervention categorisation. This was developed because we recognised that many interventions had multiple, often overlapping, components in varying amounts. Thus, rather than analyse by each component, we used the classification to allocate interventions to the best-fitting category. The classification was developed by the clinical colead investigator (Burton) and reviewed and revised during the study with the three other clinical investigators (Dawes, Deary, Newton) in the following steps:

1. A simple description of the interventions in each arm was recorded during data extraction.
2. A clinical investigator reviewed these to generate an initial classification with draft criteria for each category. The same investigator then reviewed the full-text descriptions of interventions and classified them using the draft criteria: during this process, the criteria were edited and refined following discussions with other clinical investigators.
3. Criteria were reviewed and tested (for a sample of behavioural interventions) by independent checking of categorisation. Differences were resolved by discussion.
4. The final criteria (presented below) were reapplied to all included studies. In parallel with this, we grouped the individual intervention categories into higher-level groups to produce a hierarchical taxonomy. The categories and criteria are in *Appendix 2*.

### *Statistical analysis*

The primary analysis consisted of three separate network meta-analyses (NMAs) under the transdiagnostic assumption (i.e. that data were comparable across conditions), each corresponding to a different follow-up time point. We used standardised mean difference (SMD) of the change in fatigue outcomes from baseline as the measure of effect, evaluated using Hedge's correction for small studies. Additional scenario analyses were performed to assess the effect of the choices and assumptions implemented within the primary analyses. This included a re-analysis of the long-term network to include alternative long-term follow-up data reported within studies (e.g. data reported at both 8 and 12 months), condition-specific analyses (five conditions at end of treatment, one condition for short-term follow-up, two conditions for long-term follow-up) and removal of pilot/feasibility studies from each of the primary analyses. None of the scenario analyses resulted in substantially different predicted effects. Finally, in order to translate findings from the SMD into clinically meaningful values, we took the estimated clinically important difference on the Fatigue Severity Scale (FSS)[25] and mapped it to the standard deviation in the NMA (using end-of-treatment data) to find the SMD that could be considered equivalent to the clinically important difference in fatigue.

## Cost-effectiveness analysis

The methods of this analysis are described in detail in the linked publication and summarised here.

A systematic review of published cost-effectiveness analyses identified only four papers which all reported within-trial analyses from RCTs. These covered a limited range of conditions and interventions and therefore a de novo analysis was required.

The CEA took a UK NHS and Personal Social Services perspective and evaluated costs and quality-adjusted

life-years (QALYs) over a 2-year horizon. CEA was conducted using studies which were (1) included in the clinical effectiveness NMA, (2) reported long-term follow-up effectiveness and (3) belonged to an intervention category which showed statistically significant benefits at either short- or long-term follow-up in the NMA. Only a minority of studies included in the NMA reported a measure of health utility directly. Therefore, we applied a mapping algorithm to estimate utility values from the fatigue outcomes estimated by the evidence synthesis for each category of interventions over which effectiveness estimates had been pooled. We conducted a targeted review of studies mapping fatigue measures to health-related quality-of-life measures. The most suitable model was the regression model mapping from FSS to SF-6D provided by Goodwin.[26]

### *Quality-adjusted life-years*

The QALY gains for each intervention relative to UC were estimated using an 'area under the curve' (AUC) approach based on the average time points for fatigue outcomes reported in the studies contributing to the NMA. For each intervention category, the studies included in the NMA for that category were used to estimate the timing for end of treatment and two further follow-up points (short term and long term). As it did not seem justifiable to assume a sudden return to baseline fatigue scores after the last follow-up, we assumed that interventions would experience a linear decline in treatment effect between the last follow-up and 24 months after baseline in the base case. This assumption was informed by examining long-term data from two studies reporting outcomes more than 1 year after baseline.[21,27] We applied the same effectiveness data to group and individual interventions within the same intervention category as these were pooled within the NMA. Estimated FSS scores for each intervention and comparator arm were then mapped to utility values, and the total QALYs gained were estimated for each intervention and the UC comparator arm by using the AUC method, discounted at a rate of 3.5% per annum.[28]

### *Estimation of costs*

Included studies were examined to determine the resources required to deliver the interventions. Information was extracted on the number of sessions, duration of sessions and the healthcare professionals involved in delivering or facilitating the interventions. For interventions delivered to groups, information was also extracted on the number of individuals who started the intervention, the group size and the number of groups to allow an estimation of the average cost per patient. Unit costs were taken from the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care 2023,[29] with the exception of cognitive–behavioural therapy (CBT), which was only reported in a previous edition of the PSSRU Unit Costs (2017),[30] and therefore, this cost was uplifted to 2023 prices. The median cost across a category of interventions was used in the CEA with interventions delivered to groups costed separately from those delivered to individuals. To allow comparable data to be obtained across multiple studies, the costing analysis includes only intervention costs and does not estimate the impact on other healthcare resource use, such as reduced primary or secondary care attendances resulting from patients experiencing lower fatigue or increased use from potential adverse effects.

### *Cost-effectiveness*

The CEA used expected QALY gains and the expected intervention costs described above. The net monetary benefit (NMB) was estimated based on the willingness-to-pay threshold of £20,000 per QALY gained. The cost-effectiveness estimates were evaluated both deterministically and using a probabilistic simulation to quantify uncertainty. Scenario analyses were also conducted, including exploring the impact of optimistic and pessimistic durations for the decline of treatment effect, and applying the highest and lowest intervention costs within the category.

## Qualitative evidence synthesis: experience of treatment

For both syntheses, we followed the methods outlined in the Cochrane-Campell Handbook of QES[31] and reported the review according to the recommendations of the 'Enhancing Transparency in Reporting the Synthesis of Qualitative Research statement'.[32]

### *Inclusion criteria*

We used the same condition criteria as the clinical effectiveness review, and studies were potentially eligible if they used a qualitative or mixed-methods approach; included findings about patient perspectives on interventions for fatigue; and provided a description of sampling strategy, data collection and data analyses. Following this inclusive approach, the initial pool of included studies was further narrowed down according to a list of candidate conditions identified as either featuring in key findings of the clinical effectiveness review or showing promise.

### *Information sources*

A comprehensive search of bibliographic databases to identify qualitative research was conducted in September–October 2023, with a methodological search filter selected for specificity that was used to identify qualitative studies. Given known variations of health and social systems across countries by both time and context, included studies were

limited to 2014 onwards, published in English language and conducted in English-speaking, Western European and Scandinavian countries. All searches were performed on the following databases: Ovid MEDLINE, EMBASE (via Ovid), CINAHL (via EBSCO), APA PsycInfo (via Ovid), Web of Science Core Collection (Science Citation Index and Social Sciences Citation Index). Once candidate studies were identified, systematic CLUSTER searching for sibling, related and associated studies[33] was conducted using study identifiers such as the ISRCTN and trial or study name.

### *Study selection and data collection*

Independent screening was conducted by two authors, first on study titles and abstracts and, subsequently, on the full text of selected studies. Discrepancies were resolved through a discussion between the two authors. To assess methodological limitations, we used the Critical Appraisal Skills Programme (CASP) Qualitative Checklist (CASP, 2013).

### *Synthesis*

The findings were analysed using an inductive thematic synthesis approach[34] adapted to analyse distinctive-meaning units rather than line-by-line coding.[35] Findings from the included studies were read, coded and examined for overlapping analytical themes. Findings included direct verbatim text extracts from participants and author interpretations from the results sections. Two reviewers coded a subset of studies identified for inclusion and then reconvened to discuss and establish the coding schematic for the remaining findings. After all the findings were coded, the two reviewers generated the final analytical themes and discussed them with the coauthors.

## Qualitative evidence synthesis: experience of fatigue across conditions

We carried out a mega-synthesis (overview of qualitative evidence syntheses) examining fatigue experiences across various chronic conditions. The research analysed 13 systematic reviews containing 189 individual studies, with a focus on understanding both shared and condition-specific aspects of fatigue. Initial searches covering the same time period covered by the qualitative intervention review were conducted both on Epistemonikos (a purpose-specific systematic reviews database) and on PubMed/ MEDLINE.

## Patient focus groups

We recruited five focus groups in order to reflect diversity of participants, clinical conditions and location. Each group met on three occasions during the study, in early and mid 2024 and in early 2025. We conducted the focus groups using participatory approaches that we had previously found effective in patient and public involvement (PPI) work with diverse patient groups, including using concise information summaries to inform interactive discussion and activities such as preference sorting. Ethics approval was obtained from the NHS Health Research Authority (23/SC/0292). The focus groups were co-led by an academic researcher (Fryer) and patient researchers (Coyle and McCormick).

### *Participants and recruitment*

Inclusion and exclusion criteria matched those of the systematic review (above). We used multiple approaches to ensure a diverse sample involving contacting patients through patient and other community organisations, with a focus of ethnic minority heritage. We had originally intended to recruit through specialist clinical services; however, we quickly reached capacity from the other sources, and there were considerable delays with the hospital trust research governance processes. The list of organisations contacted is in *Appendix 1*. Invitations were sent as posters/flyers as organisations permitted with the opportunity to respond via e-mail or by a dedicated phone number. Individuals who expressed an interest were then contacted and received further information prior to enrolment. Participants provided written consent before the first focus group, and this was verbally confirmed at the start of each focus group.

### *Focus groups*

Focus groups were held online (3) and in community settings (2). The first round of focus groups gave participants the opportunity to describe their experiences of fatigue and to compare and contrast experiences across conditions. The second round focused on potential interventions and involved both description of experiences and discussion about a set of vignettes of potential fatigue interventions. The third round focused on communicating results of the evidence synthesis. The content of the groups was audio-recorded and transcribed before analysis, which used thematic analysis. Developing findings were discussed within the study team.

## *Results summary*

## Quantitative systematic review

We reviewed 10,108 titles and abstracts. From these, 1068 full-text articles were assessed for eligibility, out of which 119 studies reported in 121 manuscripts were eligible for inclusion. Out of these, 88 studies, reported in 90 manuscripts, had sufficient data for inclusion in the NMA. This is summarised in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (*Figure 1*).

### *Conditions and interventions*

The category structure with numbers of studies is shown in *Figure 2*. The most common condition was MS (51

studies). There were six studies in stroke, and five in other neurological conditions. Twenty studies involved a range of musculoskeletal and connective tissue disorders ranging from osteoarthritis to systemic sclerosis. The remaining studies included inflammatory bowel disease (6) chronic kidney disease (3) and diabetes, hypothyroidism, heart disease and psoriasis (1 each).

The intervention category structure with the number of studies is shown in *Figure 3*. The most common intervention was CBT-based (19 studies). Other SM interventions were energy-conserving fatigue management (11), activating fatigue management (3) and general SM (6). Twenty-eight interventions were focused on physical activity, including supervised exercise (14), unsupervised exercise (7) and physical activity promotion (PAP) (7). There were small numbers of other interventions, including passive stimulation and nutritional interventions.

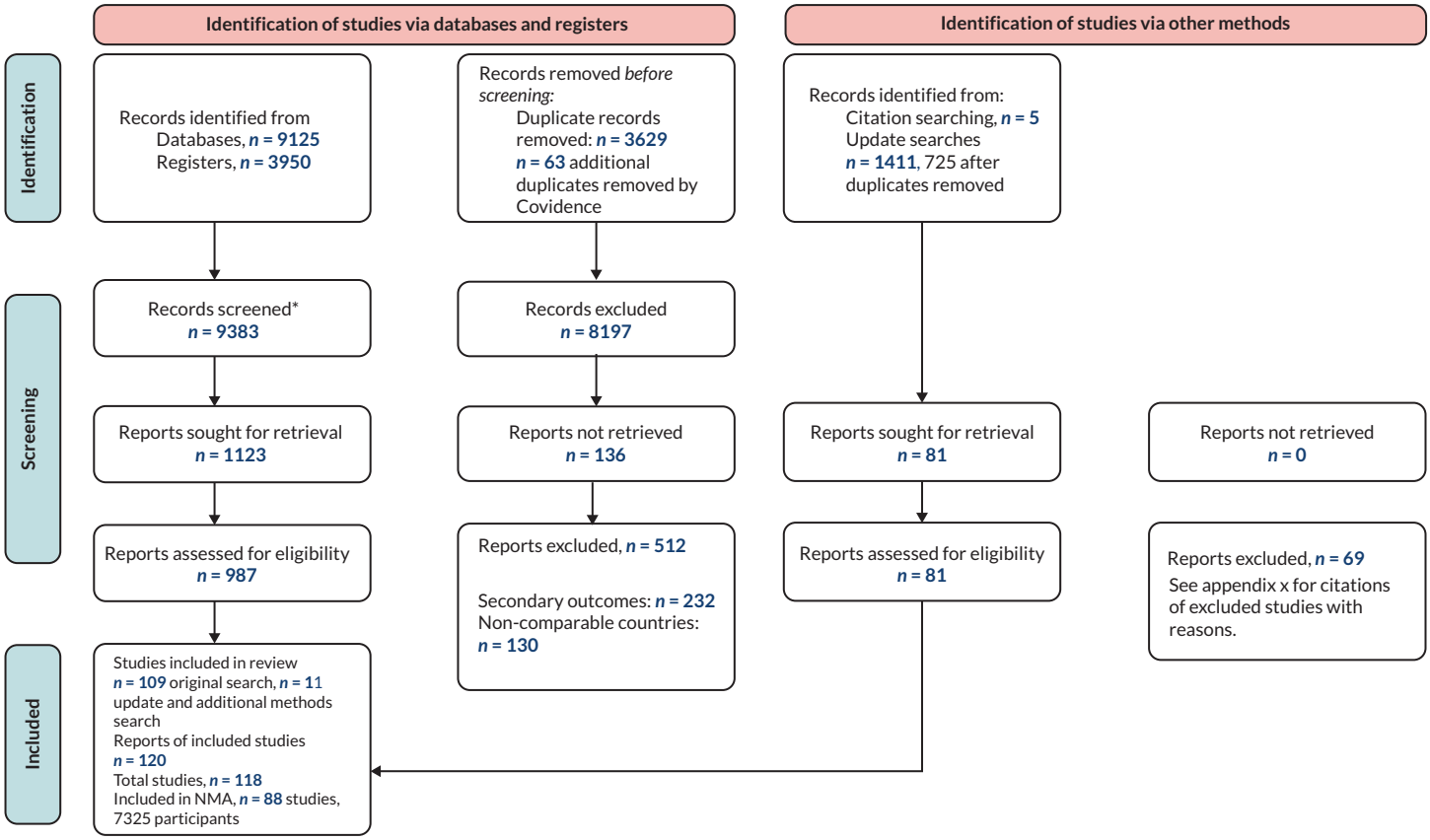
*Appendix 3*, *Figure 6* displays the relationship between intervention categories and conditions to the level of individual studies (details of which can be viewed in the clinical effectiveness paper).

### *Risk of bias*

As the majority of interventions were behavioural (either SM or activity-based) and therefore not blinded to participants, the risk of bias was generally assessed as high.

### *Network meta-analysis*

Networks for the primary analysis at the different time points are shown in *Figure 4* network geometry (a) End of treatment, (b) short-term analysis and (c) long-term analysis, respectively, indicating the number of participants who received each intervention (size of node) and the number of studies contributing to the direct evidence and comparisons between interventions (thickness of line) *Figure 4*. The networks contained 27 connected interventions (including control interventions) at the end of treatment, 16 at short term and 13 at long-term follow-up. They were evidenced from 84, 24 and 18 studies, respectively. Forest plots of the NMAs are in




*Inter-rater Cohen's kappa for title/abstract 0.58, all records were double or triple sifted.

**FIGURE 1** The PRISMA flow diagram. Reproduced with permission from Leaviss *et al.*[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY-ND 4.0) license, which permits others to copy and redistribute the material in any medium or format for any purpose, even commercially, provided the original work is properly cited. If you remix, transform, or build upon the material, you may not distribute the modified material. See: https://creativecommons.org/licenses/by-nd/4.0/deed.en. The figure above includes minor additions and formatting changes.

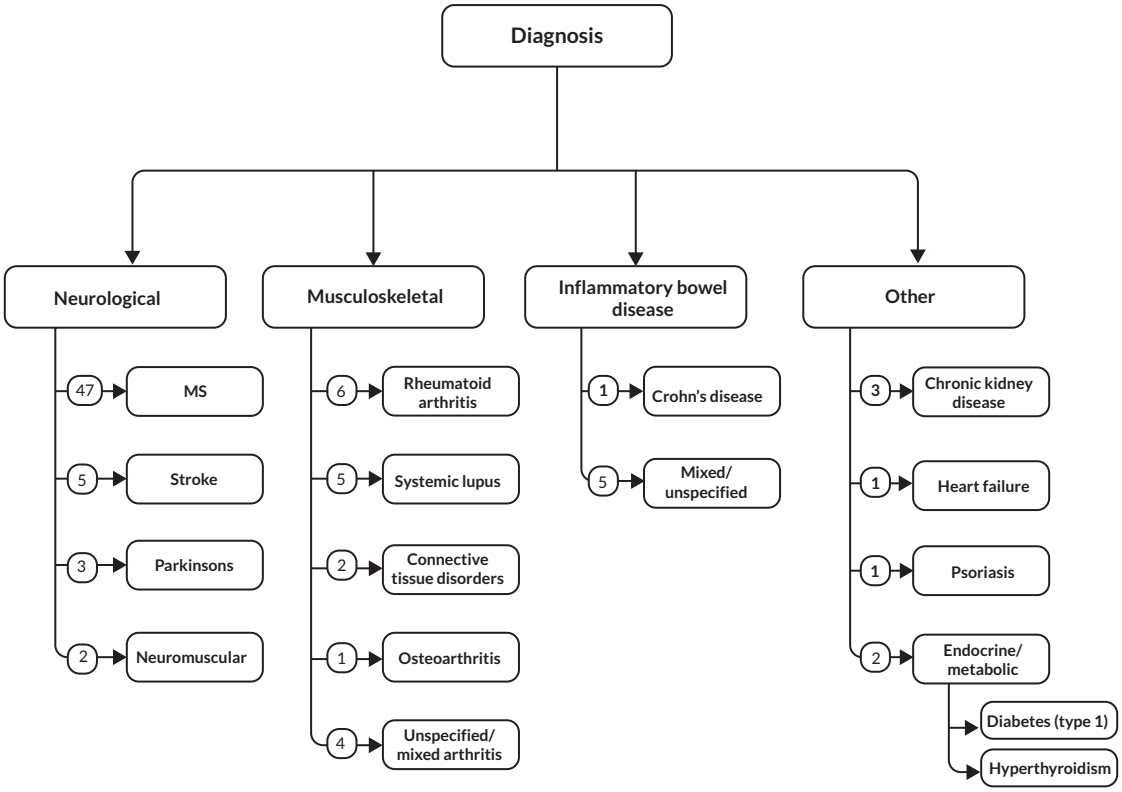



**FIGURE 2** Classification of conditions (with numbers included).

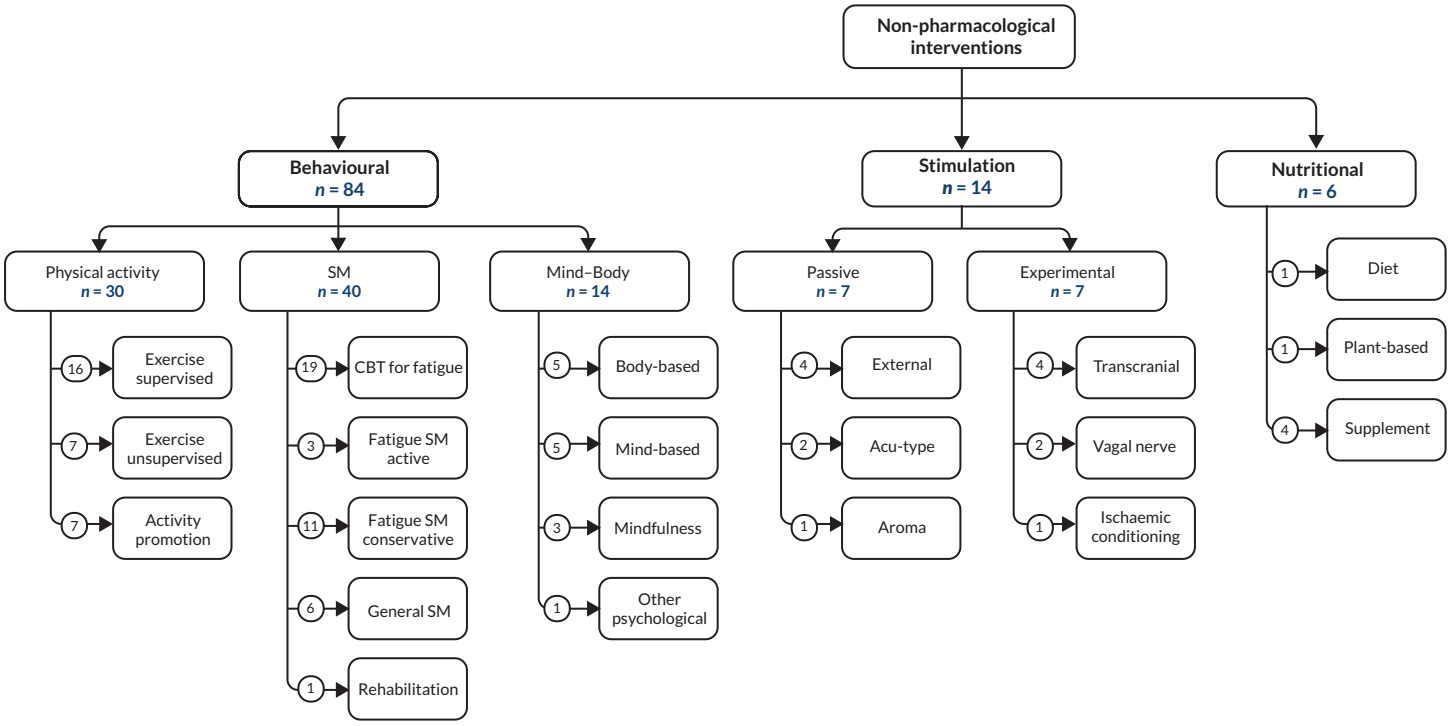
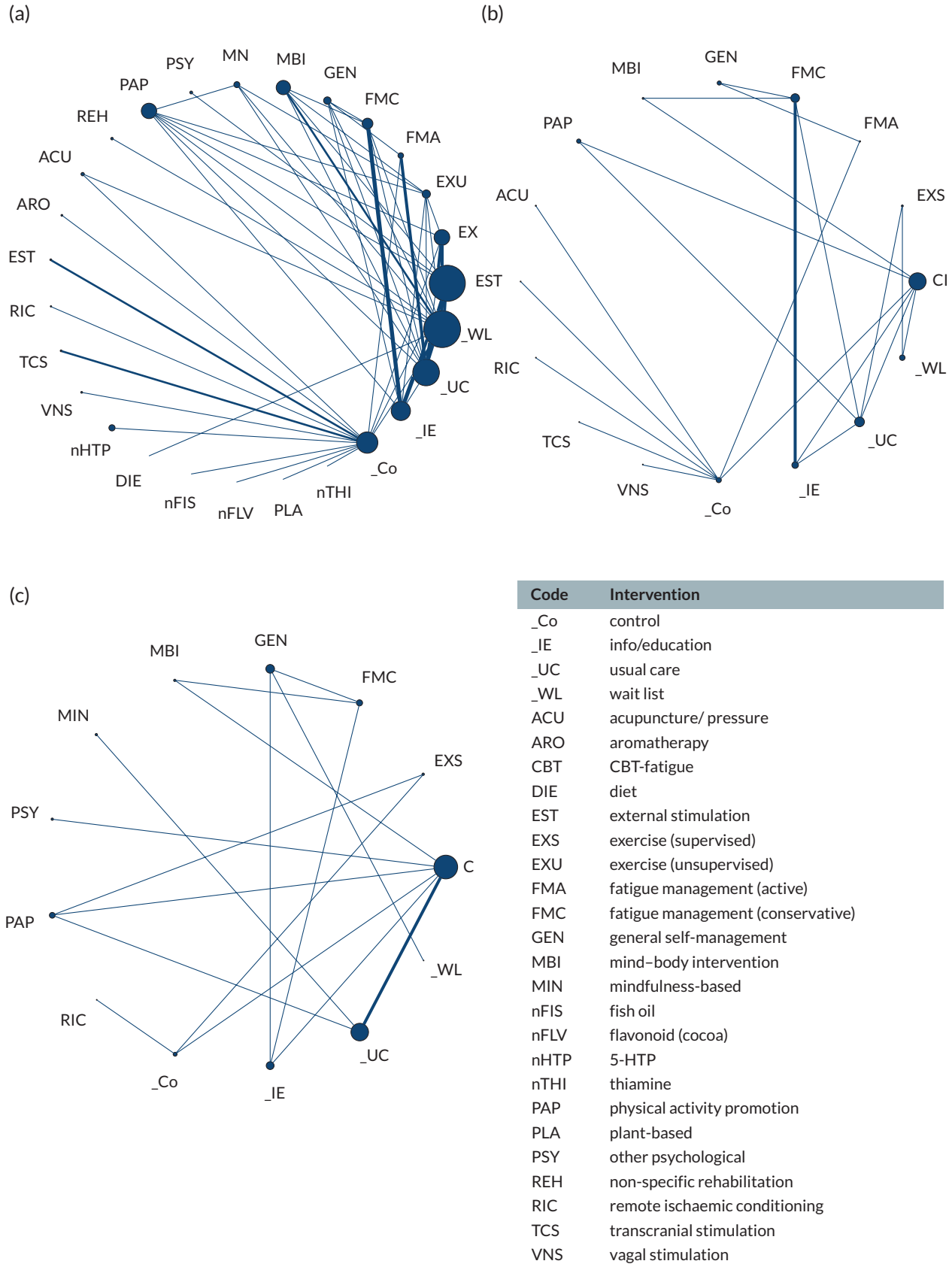



**FIGURE 3** Classification of interventions.




| Code | Intervention |
|---|---|
| _Co | control |
| _IE | info/education |
| _UC | usual care |
| _WL | wait list |
| ACU | acupuncture/ pressure |
| ARO | aromatherapy |
| CBT | CBT-fatigue |
| DIE | diet |
| EST | external stimulation |
| EXS | exercise (supervised) |
| EXU | exercise (unsupervised) |
| FMA | fatigue management (active) |
| FMC | fatigue management (conservative) |
| GEN | general self-management |
| MBI | mind–body intervention |
| MIN | mindfulness-based |
| nFIS | fish oil |
| nFLV | flavonoid (cocoa) |
| nHTP | 5-HTP |
| nTHI | thiamine |
| PAP | physical activity promotion |
| PLA | plant-based |
| PSY | other psychological |
| REH | non-specific rehabilitation |
| RIC | remote ischaemic conditioning |
| TCS | transcranial stimulation |
| VNS | vagal stimulation |

**FIGURE 4** Network geometry. (a) End of treatment, (b) short-term analysis and (c) long-term analysis, respectively, indicating the number of participants who received each intervention (size of node) and the number of studies contributing to the direct evidence and comparisons between interventions (thickness of line). Legend contains codes for each intervention. Reproduced with permission from Leaviss *et al.*[1]  The figure above includes minor additions and formatting changes.

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*Appendix 3*, *Figure 7* (end of treatment) and *Appendix 3*, *Figure 8* (short-term and long-term follow-ups).

Cognitive–behavioural therapy-based interventions showed statistically significant benefits relative to UC at end of treatment [SMD −0.63, 95% credible interval (CrI) −0.87 to −0.4, 17 studies) and long-term follow-up (−0.4, −0.63 to −0.21, nine studies). The SMD at short term, with fewer studies, was smaller (−0.17, −0.42 to 0.06, seven studies). Active fatigue management had statistically significant benefits at end of treatment −0.77 (−1.2 to −0.32, three studies), but these were not sustained to short term (two studies), and no studies reported long-term follow-up. Conservative SM showed no statistically significant benefit at end of treatment (−0.2, −0.52 to 0.12, 10 studies), short term (−0.13, −0.51 to 0.25, seven studies) or long term (−0.42, −0.9 to 0.09, seven studies). Mindfulness interventions showed benefit at end of treatment (−0.59, −0.99 to −0.18, three studies) and long term (−0.54, −0.99 to −0.11, one study).

Physical activity promotion showed significant benefit at all three time points: end of treatment (−0.32, −0.62 to −0.01, seven studies), short term (−0.51, −0.84 to −0.17, one study) and long term (−0.52, −0.86 to −0.18, two studies). Supervised exercise showed statistically significant benefit at end of treatment (−0.51, −0.74 to −0.28, 14 studies) but SMDs at short term (−0.44, −0.89 to 0.003, 3 studies) and long term (−0.41, −0.91 to 0.09, 2 studies), while of comparable magnitude, were not statistically significant.

We estimated that a clinically important difference of 3.6 points on the FSS (range 9–63)[25] was equivalent to a SMD in the NMA of 0.34. This indicates that the effect sizes which reached statistical significance were also likely to be clinically meaningful.

Other interventions were identified and included within the NMA; however, these interventions were associated with low study numbers (several intervention categories were comprised of single studies) and numbers of participants, and thus their predicted treatment effects should be interpreted with caution.

## Cost-effectiveness analysis

Based on the NMA results, PAP, CBT-based fatigue interventions (CBT-fatigue) and mindfulness were found to be eligible for our economic analysis. We chose not to include remote ischaemic conditioning in the economic analysis, as, although this did achieve a statistically significant difference in fatigue versus UC in the long-term NMA, this was based on a single study in stroke patients.

### *Quality-adjusted life-years*

Physical activity promotion was estimated to have the highest utility values at short-term and long-term follow-up time points. Analyses indicated that mindfulness and PAP interventions were associated with higher QALYs gained than CBT-based fatigue interventions.

### *Resource use and costs*

A cost was derived from at least one arm of 21 studies that included a total of 23 intervention arms that were classified as CBT-fatigue, PAP or mindfulness. Median costs ranged from £156 for group PAP to £817 for individual CBT-fatigue.

### *Cost-effectiveness*

The incremental costs and QALYs and the incremental net monetary benefit (INMB) for each intervention versus UC, using the probabilistic model, are presented in *Table 1*. Deterministic results were similar, so they are not presented here. It can be seen that for all interventions, the INMB versus UC is positive, which means that the

**TABLE 1** Summary of findings of CEA

| Intervention type | Group or individual intervention | Number of study arms | Incremental costs (£) | Incremental QALYs | INMB against UC (£) |
|---|---|---|---|---|---|
| UC | – | – | – | – | – |
| PAP | Individual | 3 | 267 | 0.060 | 934 |
| CBT-fatigue | Individual | 10 | 810 | 0.045 | 90 |
| Mindfulness | Individual | 2 | 462 | 0.061 | 760 |
| PAP | Group | 2 | 157 | 0.060 | 1045 |
| CBT-fatigue | Group | 5 | 485 | 0.045 | 415 |
| Mindfulness | Group | 1 | 214 | 0.061 | 1007 |

monetary value of the QALYs gained is greater than the intervention cost when valuing a QALY at £20,000. In both deterministic and probabilistic analyses, PAP (group intervention) is estimated to provide the highest NMB compared to UC, followed by group mindfulness, and then individual PAP. The higher cost of CBT-fatigue interventions means that they have the lowest INMB versus UC, with individual CBT-fatigue having the lowest INMB. These findings were generally robust to the scenario analyses conducted with the exception of CBT-fatigue which had a negative INMB versus UC when applying a more pessimistic assumption about the decline in treatment effect (no effect at 15 months rather than at 24 months), and when applying the highest intervention costs from studies within the CBT-fatigue category.

## Qualitative evidence synthesis

### *Mega-synthesis of the experience of fatigue in long-term conditions*

We identified four themes relating to the experience of fatigue with relevance to the nature and content of interventions:

1. The multidimensional nature of fatigue: this includes physical manifestations, cognitive dimensions and emotional aspects. There was widespread recognition that individuals experienced these in different ways and proportions, with distinct temporal characteristics (with some experiencing predictable patterns and others facing unpredictable variation).
2. Life impact and functional limitations: this included disruption of daily activities, social consequences and occupational impact. These included biographical disruption from pre-illness identity.
3. Social understanding and legitimacy: these included the invisibility of fatigue, lack of recognition by healthcare professionals, responses of family and social networks, and lack of broader societal recognition of fatigue as a legitimate condition.
4. Coping strategies and SM: this included energy conservation, psychological adaptation and acceptance, enlisting social support through education and setting boundaries, acquiring knowledge and self-advocacy skills, and physical activity – when appropriately tailored.

## Experience of fatigue interventions

From the review of patient experience of fatigue interventions, we identified the following cross-condition themes:

1. Importance of coherence and understanding

Participants across studies emphasised how understanding the biopsychosocial nature of fatigue was foundational to managing it effectively. Developing a clear understanding of fatigue as a legitimate symptom helped participants 'reframe' their experience and reduce guilt/self-blame. However, when interventions clashed with participants' existing understanding (e.g. biomedical vs. biopsychosocial), engagement was diminished

2. Process of change

Successful interventions facilitated shifts in three key areas:

- Knowledge (understanding fatigue and its management)
- Expectations (about fatigue and oneself)
- Behaviours (implementing concrete strategies)

These shifts led to outcomes like normalisation, increased self-permission to rest and greater sense of control.

3. Personalisation and applicability

Participants valued content that could be tailored to their individual circumstances. Goal-setting that focused on personal priorities was particularly valued, and effectiveness was linked to how relevant the intervention content was to participants' daily lives.

4. Barriers to engagement

Consistent findings included three forms of barrier: (1) interventions often carried a cognitive burden – many participants found written materials and concentration difficult because of their fatigue; (2) specific conditions or treatment carried specific limitations, such as time constraints from treatments (e.g. dialysis); (3) digital interventions brought technical challenges for some in terms of access and usability.

5. Social support elements

The 'power of community' was consistently highlighted across group interventions. Participants valued sharing experiences with others facing similar challenges, and validation from peers appeared therapeutic in itself, beyond the formal intervention content.

6. Delivery format considerations

There was strong evidence here of clear differences in preference among individuals in terms of mode of delivery

(online vs. in-person, individual vs. group). The relationship of timing of the intervention to point in a disease trajectory was seen as important (e.g. newly diagnosed vs. experienced). Finally, the structure of interventions needs to find a balance of frequency and duration with recognition that too little does not allow for change, while too demanding an intervention creates burden.

### *Disconfirming data*

For each theme above (and in the synthesis below), we identified items of disconfirming data. These are described more fully in the individual papers.

### Patient and public involvement focus groups

The focus groups were recruited through patient organisations and community groups, specifically targeting non-White ethnic heritage. From 44 respondents, we recruited 25 (18 women and 7 men) who were able to attend focus groups which were held in person (2 groups) and online (3 groups), each on three separate occasions. While some individuals missed one of the series of three groups, none actively withdrew. Although we intended that people stay in the same group, we allowed people to move between groups and were struck that people were keen to continue their engagement.

Ages of participants ranged from under 30 to over 70, with the most represented age group being 50–59 years. We recruited from diverse ethnic heritages, with 10 identifying as South Asian, 8 as White, 5 as African Caribbean and 2 others. Long-term medical conditions reported included kidney or liver disease (6 participants), arthritis (5) diabetes (5) diabetes, heart conditions and neurological disorders (3 each).

From the focus groups, we identified four key themes:

1. Fatigue is an invisible problem. Few people had talked constructively about their fatigue with peers or with clinicians. There was little common language or models for explanation about fatigue, and few people were aware that interventions for fatigue had been developed.
2. The experience of fatigue crosses diagnostic boundaries. Each individual's experience of fatigue was personal to them. Where similarities occurred with others, these were as much across conditions as within. Nonetheless, certain features of conditions affected the experience of fatigue or constrained the approaches that might be taken to reduce it.
3. There is no one-size-fits-all solution. Differences in the experience of fatigue extended to differences in what people had found helpful for them (or saw as appropriate to try). There were some instances of scepticism, particularly where an intervention conflicted with prior experiences or beliefs; however, in general, people were open to considering new information and to trying interventions if these were made available. Participants often ranked availability or accessibility as more important than the particular name or content of an intervention.
4. Fatigue acts as a trap. In medical consultations, patients experienced professionals focusing on what was objectively measurable (e.g. the 'tired all the time' blood panel) and passing off fatigue as a symptom of the condition rather than engaging with it as something distinct or manageable. Participants who had taken action to address their fatigue described how success required a confidence that it should be safe to feel worse in the short term. Both these features conspire to trap people in their fatigue.

The group dynamics were interesting of themselves. People clearly valued the opportunity to talk about fatigue and the shared validation this brought. At the final session, three participants from different groups reported that they had decided to try increasing physical exercise on their own initiative, with perceptible benefits.

### *Research papers*

Effectiveness of non-pharmacological interventions for fatigue in long term conditions (EIFFEL)-systematic review and network meta-analysis.[1]

Which interventions are acceptable to patients for managing fatigue in long-term conditions?: a qualitative evidence synthesis.[36]

Economic evaluation of non-pharmacological interventions for fatigue in patients with long-term medical conditions.[37]

Cost-effectiveness of non-pharmacological interventions for fatigue in patients with long-term conditions: a systematic literature review.[38]

## Discussion/interpretation

### *Principal findings and achievements per project outcome*

Non-pharmacological interventions for fatigue in long-term conditions other than MS have received relatively little attention in terms of large well-conducted randomised studies. In this review, we report the first clinical effectiveness, cost-effectiveness and QES of interventions for fatigue that take a transdiagnostic perspective.

In the clinical effectiveness review, we found evidence of effectiveness for interventions which increased physical activity (either directly by supervised exercise or indirectly through personalised coaching to promote physical activity) and for CBT-based interventions for SM of fatigue. We found no significant benefit from approaches to SM in fatigue which focused on energy conservation without activation.

In the cost-effectiveness review, we found that mindfulness, PAP and CBT-based fatigue SM were associated with QALY gains (0.061, 0.060 and 0.045, respectively). Each of these interventions provided positive NMB versus UC when valuing a QALY at £20,000. However, since group interventions are less costly than individual ones, and we assumed equivalent clinical benefit, they are expected to provide greater NMBs.

The qualitative evidence syntheses identified the need for interventions that recognised the multifaceted nature of fatigue, and the heterogeneity of experience were personalised in terms of content and delivery, respected the coherence of interventions with patients' beliefs and experience, and provided knowledge and skills in the physical, psychological and social domains.

Analysis of the patient focus groups not only informed decisions within the review to take a transdiagnostic approach to fatigue but also identified four important themes: fatigue as an invisible problem, experience of fatigue being individual rather than confined to conditions, the need for personalised approaches to treatment and the idea of fatigue as a trap from which it is difficult to escape.

### *Integration of work packages and contribution to existing knowledge*

In this section, we first describe the processes by which data were integrated, both in planning analyses and interpreting them; second, we integrate the results of different WPs; third, we review the starting assumptions for the project; and finally, we propose a new synthesis.

## Integration processes

### *Qualitative research informed our clinical effectiveness analysis*

The primary aim of the focus group study was to inform the clinical effectiveness analysis. In particular, we needed to test assumptions that:

1. Experience of fatigue in long-term conditions had transdiagnostic features.
2. Descriptions of potential interventions would make sense to participants and would be generally acceptable with no major 'sticking points'.

A secondary aim, which is still ongoing, is to reflect on the findings and use these to generate patient-facing output summaries in an accessible format.

### *Clinical effectiveness results informed our cost-effectiveness analysis*

We focused CEA on those studies which had data on long-term effectiveness and which showed benefit in the clinical effectiveness analysis beyond the end of treatment.

### *Clinical effectiveness results focused our qualitative evidence synthesis*

We selected studies for the acceptability of interventions based on interventions which showed benefit in the clinical effectiveness analysis or appeared promising at the stage of early evaluation.

## Integration of work package results

### *Triangulation of qualitative synthesis with primary qualitative research*

Our two qualitative syntheses found no reviews or primary studies with populations as heterogeneous as the conditions represented in the review. Therefore, it was important to triangulate our primary findings with the synthesis of patient experience from reviews of individual conditions. While the terms used varied, there were four key findings, described below and summarised in *Table 2*:

1. Fatigue as a multidimensional problem:
   - Strongly supported in the mega-synthesis of fatigue experiences.
   - Clearly supported in both focus groups and synthesis of intervention experiences.
2. Fatigue as different for each person (not condition-specific):
   - Most strongly supported in focus groups.
   - Clearly supported in the mega-synthesis.
   - Weakly supported in intervention experiences synthesis.
3. Fatigue as an invisible problem:
   - Clearly supported in both focus groups and the mega-synthesis.
   - Not supported or not mentioned in the intervention experiences synthesis.

**TABLE 2** Summary of triangulation of themes across qualitative methods

| Theme | Focus groups | Mega-synthesis of experience of fatigue | Synthesis of experience of interventions |
|---|---|---|---|
| Fatigue as a multidimensional problem | ++ | +++ | ++ |
| Fatigue as different for each person (rather than for each condition) | +++ | ++ | + |
| Fatigue as an invisible problem | ++ | ++ | |
| Need to tailor interventions to personal capabilities and coherence | ++ | + | +++ |

+++, main or highlighted finding; ++, clearly supported finding; +, indirectly or weakly supported finding.

4. Need to tailor interventions to personal capabilities and coherence:

    - Most strongly supported in the synthesis of intervention experiences.
    - Clearly supported in focus groups.
    - Weakly supported in the mega-synthesis.

The triangulation shows that fatigue is consistently viewed as a multidimensional and highly individualised experience across research methods. While its 'invisible' nature appears in patient-centred research, the importance of personalised interventions emerges most strongly when examining intervention experiences specifically.

### *Findings from the qualitative research were then integrated with the effectiveness evidence*

Finally, we combined the evidence of effectiveness, cost-effectiveness and acceptability (framed in terms of ease of tailoring and coherence). These are summarised in *Table 3*. This shows that:

- most interventions show good effectiveness except for conservation-based fatigue management.
- cost-effectiveness data were missing for several interventions.
- PAP appears to have the best overall profile with good ratings in three categories.
- conservation-based fatigue management shows good coherence and tailoring despite poor effectiveness.
- no intervention achieves top ratings across all four domains (i.e. there is no best buy!).

## Review of initial assumptions

In planning the study, we made three main assumptions that were tested in the different WPs. These were (1) that fatigue in long-term conditions can be considered as a transdiagnostic phenomenon; (2) that the effectiveness of interventions focused on fatigue will be comparable across the conditions with which fatigue is associated; (3) that experience of interventions will be comparable across conditions. We have framed them as assumptions rather than hypotheses as we did not explicitly test them and our framing of them evolved during the study (to increase the importance of individual heterogeneity) and also because they were instrumental in the way we conducted and interpreted analyses. Alternatively, they could be considered as programme theories.

**TABLE 3** Summary of properties of interventions

| Intervention | Effectiveness | Cost-effectiveness | Ease of tailoring | Coherence |
|---|---|---|---|---|
| Supervised exercise | + | ? | + | + |
| PAP | ++ | ++ | ++ | + |
| Group CBT for fatigue | ++ | ++ | + | + |
| Individual CBT for fatigue | ++ | + | ++ | + |
| Fatigue management (activation) | ++ | ? | + | + |
| Fatigue management (energy conservation) | – | ? | ++ | ++ |
| Mindfulness-based approaches | + | + | ? | + |

++, sufficient for strong recommendation for intervention in this domain; +, sufficient for weak recommendation for intervention in this domain; –, evidence to not recommend this intervention in this domain.

### *Fatigue in long-term conditions can be considered as a transdiagnostic phenomenon*

This assumption was largely supported. It was directly assessed in the focus group study where we asked about similarities and differences between conditions. Our groups were mixed in terms of conditions which likely facilitated this (and reduced the risk of an individual patient group claiming a distinct identity). In terms of possible interventions, few participants saw approaches as being conceptually inappropriate for people with their condition. However, they did identify contextual factors (for instance, exercise in people with motor disability or the risks of group activities for people with suppressed immune systems) that could impact the acceptability of an intervention to an individual. However, as important as the lack of distinction between conditions might be, all groups emphasised that individual heterogeneity was large and important.

### *Experience of interventions is consistent across conditions.*

We observed as much variation within conditions (individual heterogeneity) as between conditions from both the QES and the focus groups. Because of the degree of this, 'consistency of experience' is not really an appropriate term. Rather, it would be more accurate to state that the heterogeneity of experience of interventions appears to be more attributable to individual differences (both personal and social) than to specific condition characteristics.

### *Effectiveness of interventions focused on fatigue is consistent across the conditions with which fatigue is associated*

We did not formally quantitatively test this as a hypothesis, as it would have required that discrete comparisons were then subjected to meta-regression. However, we did explore this by conducting a sensitivity analysis (reported in the clinical effectiveness paper) with a set of condition group-specific NMAs. While this found that the precision of estimates of effects was generally reduced (reflected in wider CrIs), the magnitude of effects and the rank order of interventions was typically similar to the results presented within the primary analyses where data for multiple conditions were combined. As we set out to measure comparative effectiveness of interventions (relative to each other), NMA was an appropriate analysis approach.

## New synthesis: an overarching model of interventions

Fatigue in long-term conditions is common, multifaceted, personal and often invisible. Therefore, interventions to address this fatigue need to reflect this complexity and heterogeneity.

We propose that behavioural interventions consider three linked phases: stabilisation (making the most of the reduced energy and current capabilities), prioritisation (assessing coherence between treatments and personal experiences and circumstances, setting goals based on personal values); and reactivation (building more energy and capabilities). These are depicted graphically in *Figure 5* and expanded below:

1. Stabilisation (making the most of current reduced energy/capacity)
   - validation (fatigue is real, complex and different for each person; each individual's experience is legitimate)
   - explanation about fatigue that includes biological and, where appropriate, psychological or social factors
   - energy conservation/activity pacing (spending current energy wisely)
   - body regulation (learning to reduce unnecessary energy use)
   - group support (especially the sense of not being on one's own)

2. Prioritisation (assessing coherence between treatments and personal experiences and circumstances, setting goals based on personal values);
   - being explicit about values
   - assessing concordance between possible activation interventions and personal experiences and capabilities
   - goal-setting

3. Reactivation (building more energy and capacity)
   - biological – personally appropriate increases in physical activity
   - psychological – identifying unhelpful thoughts, adopting effective strategies
   - social – addressing daily life barriers and consolidating behaviours
   - group hope (seeing change in others makes it more possible for oneself)

From the clinical effectiveness review, it appears that interventions that only include stabilisation (such as SM focused on energy conservation) may engage patients and provide support, but this does not translate into measurable benefit in terms of fatigue. To obtain this, it appears necessary to include elements of reactivation. However, if these are provided without elements from

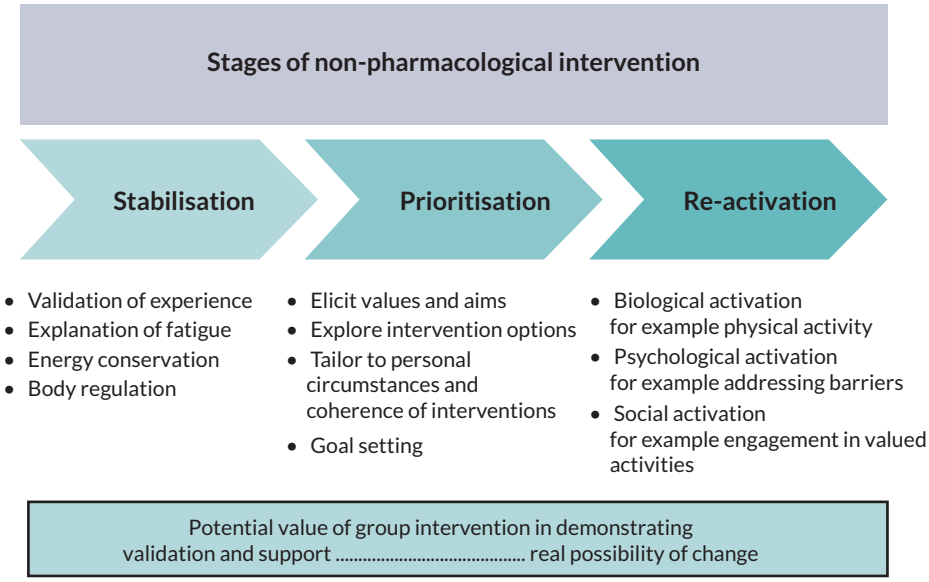


**FIGURE 5** Logic model for three stages of intervention.

stabilisation (validation, conservation, prioritisation and regulation), there is a risk of failing to achieve coherence between patient and intervention and failing to adapt the intervention to individuals' specific. Many of the CBT-based, activating SM and PAP interventions included elements of both stabilisation and reactivation.

In ordering items within these phases, it appeared from the qualitative work that validation has to come before anything else. Evidence suggested that this was a prerequisite for all that followed. We placed prioritisation as a bridge between the two phases rather than as a first step. We identified coherence between the person and their capabilities/experiences and the subsequent intervention to be important. Placing this prioritisation stage slightly later than is conventional in an intervention may provide patients' time to consider different interventions within a context of shared decision-making.

While these statements derive from data on behavioural interventions, it is likely that they will persist as important elements of the adoption of other forms of treatment. For in the example of remote ischaemic conditioning, which is persistently sui generis, participants in the single qualitative study expressed views that could be similarly coded to those for behavioural interventions.

A potential critique of this overarching intervention model for fatigue in long-term conditions could focus on several areas:

1. Evidence basis and integration concerns:
   - The model appears to synthesise findings from qualitative and effectiveness studies, but it is unclear how rigorously these were integrated or weighted.
   - The statement that interventions focusing only on stabilisation do not translate to measurable benefits seems definitive, but the evidence may be more nuanced.
   - The model makes causal claims (e.g. 'validation has to come before anything else') that may exceed what the underlying data can support.
2. Theoretical framework limitations:
   - The model does not explicitly connect to established theoretical frameworks in behaviour change or chronic illness management.
   - It is currently unclear how this model relates to or improves upon existing staged approaches to behaviour change.
   - The conceptualisation of fatigue itself (as multifaceted, personal, invisible) may limit consideration of biological mechanisms.
3. Implementation challenges:
   - The sequencing of phases (stabilisation → prioritisation → reactivation) may not reflect how people actually experience and manage fatigue and needs to be tested prospectively.
   - The model does not address how to handle setbacks or cycling between phases.
   - Little guidance is provided on how clinicians should determine when a patient is ready to move from one phase to another.
4. Measurement and evaluation issues:
   - The model does not specify how success in each phase should be measured.

- It's unclear how to evaluate whether the model as a whole is more effective than alternative approaches.

5. Personalisation paradox:
   - While emphasising personalisation, the model still prescribes a universal sequence.
   - This creates a tension between the recognition of fatigue as highly individual and the presentation of a standardised intervention approach.

In summary, the three-phase approach we propose is potentially interesting but requires more rigorous theoretical grounding, clearer operationalisation and stronger empirical support before it can effectively guide clinical practice.

## Strengths and weakness of the study

The strengths and weaknesses of individual WPs are described in their respective papers but are summarised below.

### *Clinical effectiveness review*

The strengths of this review include the broad scope of both eligible conditions and non-pharmacological interventions, the extensive search process and rigorous sifting and extraction of data. We used NMA to combine evidence across multiple conditions and interventions which enabled us to deal with the limited number of studies in all conditions apart from MS.

This review faced several limitations relating to eligibility of studies, choice of time points, use of SMDs, categorisation of interventions and the large number of small studies. As the majority of studies were of behavioural interventions, often using pragmatic designs, blinding of participants was rare, and so risk of bias was rated as high for almost all studies.

The studies identified within the review reported fatigue and fatigue change using a variety of scales, such as the fatigue severity score, and the modified fatigue impact scale, and thus the SMD was used to facilitate the synthesis of all identified studies in accordance with currently accepted practice. The use of the SMD is, however, limited to the assumption that the outcomes are approximately normally distributed within each treatment group of the studies. If this is systematically violated, then the SMD may not accurately reflect the true difference between the groups of the study and could impact the synthesised results.

The classification of intervention categories was new to this study and deliberately took a clustering approach, in which similar interventions were grouped together, in contrast to a component approach in which interventions are deconstructed to their constituent components. We did this because many interventions had multiple and often overlapping components albeit in different proportions and apparent emphasis.

### *Cost-effectiveness review*

As only a small number of studies conducted within-trial CEA, we conducted a de novo analysis which drew on the clinical effectiveness study for estimates of effect. To ensure that a consistent approach was used across studies, our analysis of costs was limited to staff time required to deliver the interventions. We included both individual and group-based interventions and assumed comparable effectiveness. While the evidence from both approaches did not refute this assumption, we had limited power to test it. Furthermore, comparability of group and individual delivery has been shown in other contexts (e.g. CBT for depression). The importance of group-based interventions in terms of cost-effectiveness is particularly relevant in the case of CBT-based interventions, where cost-effectiveness results from the within-trial economic evaluations found CBT was dominated by UC because of higher intervention costs and small negative incremental QALYs.[21,39,40] One of these studies that compared PAP to CBT directly using a within-trial analysis of the RCT[40] found that CBT was dominated by PAP, and this finding is replicated in our de novo analysis informed by effectiveness data from multiple studies.

### *Qualitative evidence synthesis*

We chose two distinct methods for the two questions, approaching acceptability through thematic synthesis of individual studies and experience through mega-synthesis of published reviews. Thematic synthesis was selected to enable systematic coding and theme development while maintaining a clear link to primary data. The method is particularly suited to synthesising evidence about intervention acceptability and facilitates integration with quantitative findings from the companion NMA.

### *Focus group study*

The strengths of this study included the heterogeneity of the groups, that is, their long-term conditions, and the role of investigators with lived experience as facilitators for the groups. There was substantial representation of traditionally underserved communities and almost complete retention of participants across the three rounds of focus groups. The use of a mix of online and in-person

community groups provided wide geographical coverage, while allowing people from under-represented groups to feel they were being heard in their own space. The limitations included a lack of people with MS and other neurological conditions. While their experiences have been more fully described in other work (and are thus captured in our QES), we missed an opportunity to test ideas of similarity directly.

### *Findings in relation to other studies*

This study is the first to take such a wide perspective of fatigue in long-term conditions, integrating clinical effectiveness, cost-effectiveness and qualitative data across multiple conditions. As such, there are few directly comparable studies. We did note two condition-specific meta-analyses in MS[41] and stroke.[42] Relative to these, we applied more stringent inclusion criteria but obtained broadly similar results.

Some comparison is, however, possible with studies in conditions out of scope of this review. This is most challenging in ME/CFS, in relation to both CBT and exercise. While the most recent systematic review found evidence for effectiveness of CBT,[43] its interpretation in guideline recommendations remains contested.[44,45] Interestingly, a recent review of activity pacing in ME/CFS (which can include both energy conservation and activity promotion) suggested some effectiveness, particularly where there are elements of increasing physical activity.[46] Work in ME/CFS and also more recently in long COVID has highlighted the importance of coherence of treatment to patient beliefs.

While few trials of interventions are designed to be transdiagnostic and highly personalised, lessons can be drawn from studies such as the Multiple Symptoms Study 3,[47] which included people with multiple persistent physical symptoms (commonly termed 'medically unexplained symptoms'). Here the consultation-based intervention comprised four elements: recognition, explanation, action and learning.[48] The validation of the individual and interpretation of symptoms as complex, real and tractable showed sustained benefit[47] along with plausible mechanisms.[49]

### *Take-home message(s)*

Fatigue in long-term conditions is common, multifaceted, personal and often invisible. Interventions to address it need to reflect this complexity and heterogeneity.

We have identified a set of processes that are found within effective interventions and can be used to tailor fatigue management to groups, settings or individuals. These processes appear – at least for many people – to follow some order, with some being prerequisites for others.

### *Reflections on the project and what could have been done differently*

Most elements of the project proceeded as intended, although the complexity of decisions about inclusion and exclusion and delays in getting consent in advance of the PPI work meant the study was always pressed for time.

The project team worked extremely well. Having two PPI coinvestigators undoubtedly helped in many ways (see *Patient and public involvement* for more details). The complementarity of clinical and methodological colead investigators was probably also beneficial, and we would recommend it for further studies in comparably complex fields.

Dealing with the complexity of interventions was more difficult than we had initially expected. While component-based analysis initially appeared attractive, we identified early on that many interventions included similar components albeit in different forms and amounts, and framed within different logics. We also found that the terms used to describe interventions were too inconsistent to be usable. The result was a considerable amount of work to develop an intervention taxonomy with sufficient rules to make it reproducible.

We originally planned to recruit PPI focus groups from three sources: patient organisations (condition-specific), community groups (focusing on communities traditionally under-represented in research) and specialist services for certain conditions. In practice, the first two were able to proceed quickly and were successful. The approach through specialist services turned out to be protracted and difficult (possibly because none of the investigators held a contract at the local acute hospitals trust), and in the end, it was not possible to recruit and conduct focus groups from this source within the time frame. Our reason for this third approach was partly as a safety net in case the other two approaches were unsuccessful in terms of numbers, or ended up recruiting only 'activist' patients involved with particular agendas. Neither of these turned out to be the case.

### *Changes during the study*

There are two changes that we made from initial plans, one during the protocol stage and one during the data extraction but before analysis. Both related to selection of studies. During the protocol stage, we made the decision to limit inclusion to studies which focused on fatigue rather than all studies which included fatigue as one of

many outcomes. During extraction, we made the decision to limit the analysis to studies from European (including Scandinavian) countries or comparable healthcare settings. These are described below.

### Limiting inclusion to studies focused on fatigue

During the searching and sifting phases of the clinical effectiveness review, it became apparent that many of the returned titles and abstracts included fatigue as one of many secondary outcomes of more general condition SM programmes. In order to focus the review on fatigue, and in consultation with our external advisory/steering group, we refined the criteria regarding studies having fatigue as the primary focus. This was in one of three ways: (1) the population was defined by the presence of fatigue and an eligible long-term condition, (2) the proposed mechanism of intervention directly affected fatigue – for instance, by increasing physical activity or addressing unhelpful cognitions and behaviours or (3) the primary (or coprimary) outcome of the trial was a measure of fatigue. This resulted in us excluding a substantial number of condition SM interventions, which may have included fatigue as one way in which a condition impacted on well-being or capabilities but lacked a specific focus on fatigue. A small number of interventions of this type were included by way of a primary or coprimary outcome but showed no significant benefit. We also found that the closest comparable intervention – fatigue management through energy conservation – had no effect. This omission, therefore, appears to have been justified. Similar issues were encountered with the qualitative intervention review. The earlier precedent allowed us to differentiate interventions that included fatigue among multiple symptoms, for example, anxiety, stress, depression and so on, from those specifically targeting an identified fatigue component. This form of intensity sampling explains why a large proportion of named packages include fatigue within their study label.

### Exclusion of non-comparable setting studies

The search identified a large number (approximately 130) of studies from settings not comparable to the UK or Europe – in particular, middle- and lower-income countries. After considerable discussion, we chose to exclude these because the setting was not sufficiently comparable to European healthcare systems. We also observed that these tended to be small (typically 10–20 persons per arm), testing non-mainstream interventions (e.g. aromatherapy, massage) and only reporting immediate end-of-treatment outcomes. Many of these reported what appeared to be unfeasibly large reported effects (e.g. SMD 1–1.5). While many of these were reported in a way that matched the PRISMA guidelines, we were nonetheless concerned that the research environment in which these studies had been conducted might have inherent issues that reduce the plausibility of the results. These include differences in terminology, the use of verbal collection of outcome measures by those delivering the intervention (due to low literacy and follow-up in the treatment setting) and cultures of positive affirmation towards authority that may have introduced substantial bias. One of us (Leaviss) raised this in evidence-based medicine forums and became aware that reviewers of other symptom-based topics have experienced similar patterns of study. This problem became apparent during data extraction and at the stage of preliminary analysis. As with the setting of inclusion limits, this issue was extensively discussed within the team, including the external advisory/steering committee.

We, therefore, took the decision to restrict our analysis to studies from UK, Europe (including Scandinavian countries), North America, Australia and New Zealand. This had the advantage of ensuring that the findings of the review were translatable to clinical services within the NHS as well as reducing the risk of possible bias. A similar decision had already been taken for the qualitative reviews in recognition of the sensitivity of qualitative research to societal and health services contexts.

### Integration of findings

The protocol described integration of data from different sources to a matrix representing the Feasibility, Appropriateness, Meaningfulness, Effectiveness model. In integrating the data, it became apparent that there was insufficient evidence regarding the domains of Feasibility (relating to practicability) and Appropriateness (relating to clinical settings). As a result, our synthesis focuses on meaningfulness (which we report as coherence), effectiveness and cost-effectiveness.

## *Engagement with partners and stakeholders*

### Patients and communities

This project had extensive PPI, and this is described both in the sections relating to the focus groups and in *Patient and public involvement*.

### Professional experts

Our investigator team included experts in rehabilitation (Dawes), clinical medicine (Newton, Burton) and clinical psychology (Deary). We also engaged with national and international experts through our oversight committee: Professors Basu (clinical medicine, chair), Knoop (psychology, the Netherlands), Löwe (psychosomatic medicine, Germany), Seers (nursing). This ensured diverse

perspectives being brought to the review and also potential access to networks for dissemination.

### *Individual training and capacity-strengthening activities*

Within the project, we provided career development support for early career researchers in statistics (Daly) and economics (Yee) and for an academic clinical fellow in general practice (Dwivedi). We also provided training and support (through Fryer) for our two PPI coinvestigators (Coyle and McCormick), which meant that they led the PPI focus groups in a way that was highly effective.

### *Institutional capacity strengthening*

This project strengthens institutional capacity within the Sheffield Centre for Health and Related Research at the University of Sheffield in conducting multimethods reviews in complex and contested areas of health care. It follows the previous HTA-commissioned review on behavioural interventions in medically unexplained symptoms[50] and aligns with successful primary research.[47] The extensive PPI work and the collaboration with community organisations around was designed, and so far has proved, to be sustainable by building links which stay open and valued beyond the duration of the project.

## Patient and public involvement

### *What form did the patient and public involvement take and at what stages did it occur during your study?*

#### Informing study design

During the pre-funding phase, we carried out PPI activities to recruit PPI coinvestigators and as preliminary work that looked at the transdiagnostic nature of fatigue. Given that the assumptions from this were generally supported by the more rigorous focus group work, this was valuable in itself.

#### Role of patient and public involvement coinvestigators

The two PPI coinvestigators (Coyle, McCormick) facilitated the focus groups, contributed to their analysis, constituted a PPI team within the project which met regularly (comprising Coyle, McCormick, Fryer and Dwivedi) and contributed as equal partners to monthly project team meetings. Both had substantial experience of PPI work but were supported during the project to extend this to include leadership, analysis and interpretation of the focus groups.

#### Focus groups

As these were a core element of our research, the methods and results of these are described in previous sections. However, there are a few notable points:

##### *Recruitment strategy*

We aimed to recruit widely and were largely successful in this. We prepared posters, flyers and e-mails which were co-designed and received ethical approval. Adding a dedicated phone number for response was suggested and turned out to be valuable in getting responses from typically underserved groups. We originally considered constituting focus groups according to shared features (conditions or demographics) but, in the end, allowed mixed groups based on availability in terms of time or place. We did not perceive any negative impact on participation of this, and given the transdiagnostic approach and the emerging focus on the importance of personalisation, this approach was beneficial.

##### *Serial focus groups*

Typically, focus groups in health research are constituted as one-off phenomena. For this study, participants took part in a series of focus groups with very few dropping out. This structure allowed us to use the first focus group primarily for people to give their own accounts, and this was valued. It allowed participants' usually invisible fatigue to be visible and validated. Several participants commented this was far preferable to starting with the researchers' agenda.

##### *Leading with lived experience*

Focus groups were always led by one or both of the PPI coinvestigators who were open about their lived experience of fatigue. This was valued by the participants and appeared to increase participants' engagement. The configuration of the PPI team ensured that both PPI investigators felt well supported in the work.

### *What impact did patient and public involvement have during the study? How was it useful?*

The PPI work was originally conceived as a way of testing the assumptions for the analysis but extended to become an additional source of triangulation for emerging findings and providing additional information that could not be easily derived from the evidence syntheses.

#### Testing assumptions for analysis

The first round of focus groups looked at similarities and differences in the experience of fatigue across conditions. Most participants did not see problems with bringing together research findings from different

conditions. The second round of focus groups looked at perceptions of interventions to explore acceptability. We found no consistent issues with particular interventions or professionals involved in them being more or less acceptable than others.

### Triangulation

The focus groups provided valuable triangulation for ideas developed within the QES about the importance of variation between individuals rather than between conditions. While our preliminary work had focused on similarities between conditions, this highlighted the extent and importance of tailoring of interventions to individuals. This, in turn, was strongly informative of our conclusions about the importance of personalisation and choice.

### Additional information

Focus groups provided additional information about the importance of validation (not least through people describing how participation in the groups themselves provided that) and of language for talking about fatigue. Focus groups emphasised the importance that people place on past experiences to help them make choices about the potential interventions (something absent from much of the literature which focused on single interventions), and also foregrounded practical issues (location, timing, parking and transport) that beset delivery of interventions. Finally, the focus groups demonstrated that people with diverse conditions and experiences of fatigue were open to information about different interventions and the opinions of others and developed their own views iteratively rather than from dogmatic preconceptions.

### *The way(s) patient and public involvement will support dissemination of the results*

The final round of PPI focus groups addressed this and provided several priorities for dissemination.

- Healthcare practitioners need to be more aware of the prevalence and experience of fatigue. There is a need for a language for speaking about fatigue with patients in a way that is validating and supportive.
- The problem, and what can be done to alleviate it, needs to be in the public domain. Participants described a range of places for heightening visibility, including healthcare settings, faith and community spaces, and leisure centres and other physical activity settings.
- There is a need for recognition of fatigue in the workplace. Participants emphasised the variability and unpredictability of fatigue. Further work needs to find ways to accommodate this within work without the current polarities of in work or not.

In addition to these patient-led priorities for dissemination, we have PPI participants who are willing to contribute to public dissemination materials planned for this project, including taking part in short videos.

## Equity diversity and inclusion

While this work was primarily a mixed-methods synthesis and dependent on published data, there are three areas of particular relevance to this review.

### *Focus group participants*

We recruited a highly diverse group of participants as described in the Results Summary above.

### *Research team*

There was an equal gender balance in the six members of the project leadership group (chief investigators and WP leads). Out of the 18 members of the extended research team, 13 were women. First authorship on all papers apart from the qualitative evidence syntheses will be by non-professorial researchers.

### *Included studies*

In order to produce transferability to the NHS context, we limited inclusion to studies from European or comparable cultures and healthcare settings. While justifiable in the context of the commission, this may have limited the views of people from minoritised groups. Relatively few studies reported ethnicity, education status or income of participants. In contrast, our PPI work (see *Patient and public involvement*) did include people from diverse backgrounds, and in this context, the alignment of findings between the evidence synthesis and the focus groups is both informative and reassuring.

## Impact and learning

### *Plans for dissemination and impact*

### Academic dissemination

We have submitted three papers as agreed in the publication plan: the clinical effectiveness review, the cost-effectiveness evaluation and the QES. In addition, we have submitted a systematic review of prior cost-effectiveness studies, and have two more papers from the one from the qualitative mega-synthesis and one from the focus groups study in development. We will be presenting the study at conferences this year, including the European Association for Psychosomatic medicine (two papers) and conference relating to evidence synthesis.

This synopsis should be referenced as follows:
Leaviss J, Booth A, Coyle D, Daly G, Davis S, Dawes H, *et al*. Effectiveness of non-pharmacological interventions for fatigue in adults with long-term conditions: a synopsis of the EIFFEL mixed-methods evidence synthesis. *Health Technol Assess* 2026;**30**(53). https://doi.org/10.3310/GJCB1006

### Policy and practice dissemination

We are beginning to examine approaches to disseminate the findings to practitioners and policy-makers. This will include both UK organisations, such as the Royal College of Physicians, and through European conduits, such as the EURONET-SOMA network of research and innovation.

### Public dissemination

We are preparing funded dissemination work, which will include public-facing written summaries of the work and high-quality short videos suitable for use on health or public platforms. We will continue to engage with our PPI participants to ensure these are strong.

#### *Lessons learnt for future research*

This study has demonstrated the feasibility and value of strong PPI in the design and conduct of evidence synthesis, particularly in under-recognised conditions where there is no distinct public voice.

#### *Potential impact*

Fatigue is common in long-term conditions; this study has the potential to increase the provision of and access to interventions which make a clinically important difference and which are clearly cost-effective.

## Implications for decision-makers

Fatigue in medical conditions is common and is currently a hidden disability. Patients do not talk about it because clinicians do not respond (constructively) to it. There is a need to bring fatigue in long-term conditions into the open, along with a conversation which carries an appropriate degree of optimism about the possibility of change. This will require engagement with public discourses, education of professionals and commissioning of appropriate services to support patients – recognising that appropriate group-based interventions are clinical and cost-effective.

There is evidence for CBT and PAP as core interventions. However, these are typically included in a package with multiple components, so they are not just 'therapy' or 'exercise'. Our synthesis provides a framework for interventions indicating important mechanisms that should allow services to configure their own intervention based on needs and capacity.

In order to ensure people with fatigue know they are being taken seriously, it is important to recognise that the experience of fatigue is multifaceted (it is much more than 'tiredness'), and appears to be shaped by individual factors to be different for each person. For most people, it varies in time, and for many, this variation is unpredictable, creating additional uncertainty. The individual nature of fatigue means that while interventions can help, there is no one-size-fits-all solution. Patients often find the cognitive and physical work of interventions challenging – it is an extra burden at a time of limited capacity. Interventions need to recognise and respect this.

## Research recommendations

We recommend the following topics for future research and innovation.

#### *Feasibility and effectiveness of a transdiagnostic fatigue services*

This is likely to be a pragmatic RCT with the exact intervention to be decided. It may be 'pure CBT' or PAP or include elements of patient-preference design. It should include more than one clinical specialty (e.g. rheumatology, renal medicine, inflammatory bowel disease) and should consider the benefits of group delivery.

#### *Fatigue interventions in under-researched conditions*

The evidence so far has been significantly influenced by studies in neurological conditions, with very few studies in heart failure, chronic lung disease, obesity/type 2 diabetes or multimorbidity. Given the evidence for fatigue and response to interventions crossing conditions, and given that several of our focus group members had one of these under-researched conditions (in relation to fatigue) and saw them as in scope, we recommend studies which focus on delivering interventions for fatigue in one or more of these conditions.

#### *Fatigue interventions in people with multiple long-term conditions (multimorbidity)*

Despite fatigue being a powerful factor in poor quality of life in people with multimorbidity, we found no trials of interventions for people with multimorbidity. Given our transdiagnostic model, it seems appropriate to develop and test fatigue interventions for people with multimorbidity.

#### *Platform trial for investigating emerging non-invasive stimulation interventions*

While the evidence so far for non-invasive stimulation are at an early stage, there is some evidence of effectiveness, and there are plausible mechanisms as to why they may be effective. At this stage of development (where there are several potential candidates but no obvious single best intervention to test), a platform trial may permit testing of a range of interventions, and there may be value in linking

to a more mechanistic evaluation (e.g. through the NIHR Efficacy and Mechanism Evaluation programme).

### *Communication about fatigue*

Issues regarding communication about fatigue emerged from the qualitative evidence syntheses and the focus group. For professionals to adopt new approaches to explanation, there is a need to find the most constructive ways of doing this and demonstrate their effectiveness so they are not just anecdote or opinion.[48] Studies focusing on the content or delivery of explanation and support could use a range of methods (including linguistic or conversation analysis) to design and evaluate consultation content (including validation, constructive explanation, personalisation and providing confidence about interventions). This work could be stand-alone or embedded in one of the other study designs.

### *Testing and improving the three-stage model*

Our model has been derived from the evidence synthesis but not prospectively tested. Research questions related to the model could be integrated within, for instance, transdiagnostic intervention trials.

## Conclusions

Interventions for fatigue, which are based on CBT, or primarily aim to increase physical activity, are effective in reducing fatigue in people with long-term medical conditions. The average effect size is at the level of clinically important difference. There is some evidence for effectiveness of mindfulness-based interventions, but there are fewer studies of this. There is evidence that fatigue SM that aims to conserve energy without subsequent activation is ineffective. Overall, the evidence base is relatively small, heterogeneous and includes studies at moderate to high risk of bias; however, the magnitude of effect appears similar across a wide range of conditions.

In terms of cost-effectiveness, CBT-based interventions, PAP and mindfulness interventions all demonstrated the potential to be cost-effective versus UC, particularly when delivered in a group format.

The qualitative findings (evidence syntheses and primary analysis) show that fatigue in the long term is a multi-dimensional problem which is experienced differently for each person (at least as much as for each condition). While the lack of services for and discussion of fatigue means it often remains an invisible problem, interventions can be delivered in ways that are tailored to personal capabilities and coherent with an individual's experiences and beliefs. While no interventions are ideal for everyone, people with fatigue in long-term conditions generally value discussion of and access to interventions, particularly when these are delivered in accessible and convenient ways that do not place too large a burden on already limited physical and cognitive resources.

Rather than a simple recommendation for specific therapies, we hypothesise that interventions should be built around three stages: *Stabilisation* (including validation, explanation and energy conservation), *Prioritisation* (assessing coherence between treatments and personal experiences and circumstances, setting goals based on personal values) and *Reactivation* (which can include personally appropriate increases in physical activity, identifying unhelpful thoughts, addressing daily life barriers and adopting and consolidating effective behavioural strategies). We recommend that further research tests these hypotheses.

## Additional information

### *CRediT contribution statement*

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## Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

## Ethics statement

Ethics approval was obtained for the focus group study from NHS Health Research Authority, South Central – Hampshire B Research Ethics Committee reference 23/SC/0292 (12 January 2024).

## Information governance statement

The University of Sheffield is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, The University of Sheffield is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights, and the contact details for our Data Protection Officer here: https://sheffield.ac.uk/govern/data-protection/privacy/general

## Disclosure of interests

***Full disclosure of interests:*** Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/GJCB1006.

***Primary conflicts of interest:*** Andrew Booth is a former member of the National Institute for Health and Care Research (NIHR) Health and Social Care Delivery Research (HSDR) Funding Board (2019–22) and the NIHR Evidence Synthesis Advisory Group (2019–22). In 2023, he served on the NIHR SEISMIC Funding Board. He has received funded travel and accommodation from the World Health Organization for attendance at methodological guidance meetings on complex interventions (2017–8) and to attend as a technical expert, not panel member, at WHO guideline meetings. However, none of these guidelines relate to the topic of this report. His institution (the University of Sheffield) annually generates income from external short courses that he leads, including on qualitative synthesis methods.

Christopher Burton was a member of HTA advisory panels 2015–20. He receives publishing royalties for 'The ABC of medically unexplained symptoms' (Wiley 2012).

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This synopsis was published based on current knowledge at the time and date of publication. NIHR is committed to being

inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

## *Study registration*

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## *Award publications*

This synopsis provided an overview of the research award *Effectiveness of Interventions For Fatigue in Long term conditions (EIFFEL)*.

Other articles published as part of this thread are:

Leaviss J, Forsyth JE, Booth A, Coyle D, Daly G, Davis S, *et al*. Effectiveness of non-pharmacological interventions for fatigue in long term conditions: systematic review and network meta-analysis. *BMJ Med* 2026;**5**:e001746. https://doi.org/10.1136/bmjmed-2025-001746

Booth A, Rooney G, Sutton A, Leaviss J, Deary V, Dawes H, Burton C. Which interventions are acceptable to patients for managing fatigue in long-term conditions?: a qualitative evidence synthesis [published online ahead of print December 8 2025]. *Disabil Rehabil* 2025. https://doi.org/10.1080/09638288.2025.2593188.

Davis S, Mon-Yee M, Sutton A, Leaviss J, Forsyth JE, Burton C, *et al.* Cost effectiveness of non-pharmacological interventions for fatigue in patients with long-term conditions: a systematic literature review. *Expert Rev Pharmacoecon Outcomes Res* 2025;**25**:1159–66. https://doi.org/10.1080/14737167.2025.2537194

Mon-Yee M, Burton C, Leaviss J, Forsyth JE, Daly G, Davis S. Model-based economic evaluation of non-pharmacological interventions for fatigue in patients with long-term medical conditions in the UK. *BMJ Open* 2026;**16**:e102846. https://doi.org/10.1136/bmjopen-2025-102846

For more information about this research, please view the award page (www.fundingawards.nihr.ac.uk/award/NIHR154660).

## *Additional outputs*

### Planned publications

Patients' experience of fatigue in long term medical conditions: megasynthesis of qualitative evidence syntheses.

Patient's experience of fatigue in long term medical conditions: qualitative focus group study.

### Conference Papers

Interventions for Fatigue in medical conditions: systematic review and network meta-analysis European Association for Psychosomatic Medicine, Munich 2025. https://doi.org/10.1016/j.jpsychores.2025.112224

Patients' experience of fatigue in long-term medical conditions: a focus group study: European Association for Psychosomatic Medicine, Munich 2025. https://doi.org/10.1016/j.jpsychores.2025.112223

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## List of abbreviations

| | |
|---|---|
| APA | American Psychological Association |
| AUC | area under the curve |
| CASP | Critical Appraisal Skills Programme |
| CBT | cognitive–behavioural therapy |
| CEA | cost-effectiveness analysis |
| CFS | chronic fatigue syndrome |
| CINAHL | Cumulative Index to Nursing and Allied Health Literature |
| EIFFEL | Effectiveness of Interventions for Fatigue in Long term conditions |
| EMBASE | Excerpta Medica dataBASE |
| FSS | Fatigue Severity Scale |
| INMB | incremental net monetary benefit |
| ME | myalgic encephalomyelitis |
| MEDLINE | MEDical Literature Analysis and Retrieval System |
| MS | multiple sclerosis |
| NIHR | National Institute for Health and Care Research |
| NMA | network meta-analysis |
| NMB | net monetary benefit |
| PAP | physical activity promotion |
| PPI | patient and public involvement |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| PSSRU | Personal Social Services Research Unit |
| QALY | quality-adjusted life-year |
| QES | qualitative evidence synthesis |
| RCT | randomised controlled trial |
| RoB2 | Cochrane risk-of-bias tool |
| SM | self-management |
| SMD | standardised mean difference |
| UC | usual care |
| WP | work package |

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# Appendix 1 Organisations approached for patient and public involvement

**1. Neurological disorders**
NIHR Devices for Dignity Theme Leads & PPI team
MS Society
Stroke Association
Parkinsons UK

**2. Inflammatory disorders**
National Rheumatoid Arthritis Society
Versus Arthritis
Crohn's and Colitis UK
Guts UK

**3. Metabolic/other group**
National Kidney Federation
Kidney Research UK
Kidney Care UK
Polycystic Kidney Disease Charity
NIHR Devices for Dignity Renal Theme
British Heart Foundation
Asthma + Lung UK

**4. Community groups**
Deep End PPI group (South Yorkshire)
Ethnic Minorities Research Inclusion Group
Sheffield African Caribbean Mental Health Association (SACMHA)
Sheffield Chinese Community Centre
Shipshape Community Hub (Sheffield)
Care in Young People's Futures
Israac Somali Community Association
Maan Somali Mental Health (Sheffield)

# Appendix 2 Intervention classification criteria

## Physical activity-oriented interventions

### *Exercise supervised*
Multiple sessions involving physical activity in a supervised/observed environment. Can include familiarisation with exercise, addressing barriers to exercise in addition to physical activity aimed at increasing exercise capacity/strength or fitness. May include recommendations to continue between sessions. May be delivered in groups or 1 : 1. May be in a gym, community resource or outdoors. May include advice to repeat at home. Excludes specific forms of activity around training, for example, balance.

### *Exercise home*
Unsupervised exercise at home aimed at increasing exercise capacity/strength or fitness. May involve initial explanation of physical activity and addressing barriers to exercise. Includes ongoing contact/review to adapt exercise through the programme. May include initial or occasional observed sessions. May take place at home or at other personally relevant location.

### *Physical activity promotion*
One or more sessions aimed at increasing physical activity by addressing barriers to exercise, goal-setting and encouraging greater physical activity. May involve motivational techniques, cognitive/behavioural features, reporting and feedback, or the use of activity sensors. Less focused on structured exercise regimen than Exercise-Home.

### *Active recreational*
Engage in physical activity generally used as recreation – includes hippotherapy, dance and interventions involving specific therapeutic environment. Combine body-based activity with indirect positive mental well-being.

## Self-management interventions

### *Cognitive–behavioural therapy-based fatigue intervention*
Multiple sessions, focused on reducing and adapting to fatigue. May include other symptoms or aspects of the condition. Content includes (1) discussion of helpful/unhelpful thoughts and beliefs (2) behavioural activation – this may include increasing physical activity, management of time/resources and body/emotion regulating activities (3) tasks/homework between sessions. May be 1 : 1 or in groups, in person or online. May include second-generation features, such as Acceptance and Commitment. Can include mindfulness as long as it clearly meets CBT definition.

### *Fatigue self-management activation*
One or more sessions focused on adapting to fatigue and increasing overall activity/engagement. Has only limited emphasis on energy conservation. Includes encouragement to increase activity – either social (behavioural activation) or physical (explicitly increasing physical activity). May include isolated CBT component such as thought challenges but does not meet sufficient criteria for CBT.

### *Fatigue self-management: energy conservation*
One or more sessions focused on adapting to fatigue. Primary focus is on energy conservation and prudent allocation. Does not explicitly encourage increase in overall physical or social activity or set out to challenge thoughts. Includes activity pacing and other energy conservation concepts.

### *General/condition-specific self-management*
Multiple sessions focused on SM of specific medical condition/disability. May include condition-related fatigue, but that is not the primary focus (see *Fatigue self-management: energy conservation*). Includes condition monitoring/specific self-care.

### *Rehabilitation*
Multiple sessions focused on rehab from medical condition/disability. Has specific focus on either function or condition.

## Mind and body interventions

### *Body–mind*
Multiple sessions at least partly supervised which use approaches to maximise body–mind connection. Can involve traditional methods (yoga, tai-chi) or 'scientific' methods, for example, neurofeedback. Emphasises control of the body (contrast with mindfulness which emphasises control of the mind). Also includes Pilates and Exercise-Breathing, where slow movement and controlled breathing are combined.

### *Mind–body*
Interventions focused on mental relaxation/control (contrast with body–mind). Includes relaxation, imagery and so on.

### *Mindfulness-based stress reduction*
Multiple contacts focusing on learning and applying mindfulness-based techniques (meditation/breathwork). May include general guidance on living within energy resources, sleep, mental health and social interaction. Main focus is on applying mindfulness to daily life (rather than explicitly on addressing fatigue – which would be categorised as CBT with mindfulness).

### *Psychosocial adaptation to condition*
Psychosocial intervention focused on adapting to emotional consequences of medical condition. Less explicit structure and content than CBT, more focus on emotional consequences and less on other behavioural factors than living well/rehabilitation.

### *Other specific psychological therapy*
Multiple sessions, focused adapting to medical condition without specific focus on fatigue. Includes condition-focused cognitive therapy and problem-solving.

## Stimulation interventions

### *Central nervous system stimulation*
Use of one or more sessions of external stimulation of the nervous system either transcranially or via peripheral nerves.

### *External stimulation*
Application of detectable or undetectable external stimulation of the body (includes vibration, heat, light, electromagnetic force).

### *Aromatherapy*
Intervention defined as aromatherapy.

### *Touch-based*
Therapies that involve the direct (or indirect) use of human touch/interaction. Includes massage, Reiki and so on. Typically delivered in Centre for Addiction and Mental Health settings. May include passive movement.

### *Acupuncture type*
Interventions using traditional Chinese anatomical framework to deliver stimulation – acupuncture, acupressure and so on.

## Nutritional interventions

### *Plant-based*
Non-pharmacological supplement described by source rather than ingredient (e.g. paeony extract, ginseng).

### *Nutritional supplement*
Non-pharmacological supplement described by ingredient rather than source (L-carnitine, vitamins).

### *Diet*
Specific dietary intervention (e.g. low-GI, anti-inflammatory).

## Education/information

### *Information*
Provision of written/digital information with no more than one session of personal contact.

### *Education*
Provision and discussion/tailoring of written/digital information with more than one session of personal contact.

## Control definitions

### *Usual care*
Usual care or equivalent term either explicit or clearly implied.

### *Waiting list control*
Use of waitlist control. Note can include both crossover design (where arms cross over and all followed to final follow-up and parallel with no follow-up of second-arm active intervention).

### *Placebo*
Use of inert ingested substance.

### *Sham*
Use of inert external procedure.

### *Control*
Includes attentional control (presumed inert activity to adjust for time/attention), unfocused discussion meetings and activities (e.g. writing). Also used as default term if not sufficiently clear.

This synopsis should be referenced as follows:
Leaviss J, Booth A, Coyle D, Daly G, Davis S, Dawes H, *et al*. Effectiveness of non-pharmacological interventions for fatigue in adults with long-term conditions: a synopsis of the EIFFEL mixed-methods evidence synthesis. *Health Technol Assess* 2026;**30**(53). https://doi.org/10.3310/GJCB1006

## Appendix 3 Additional figures

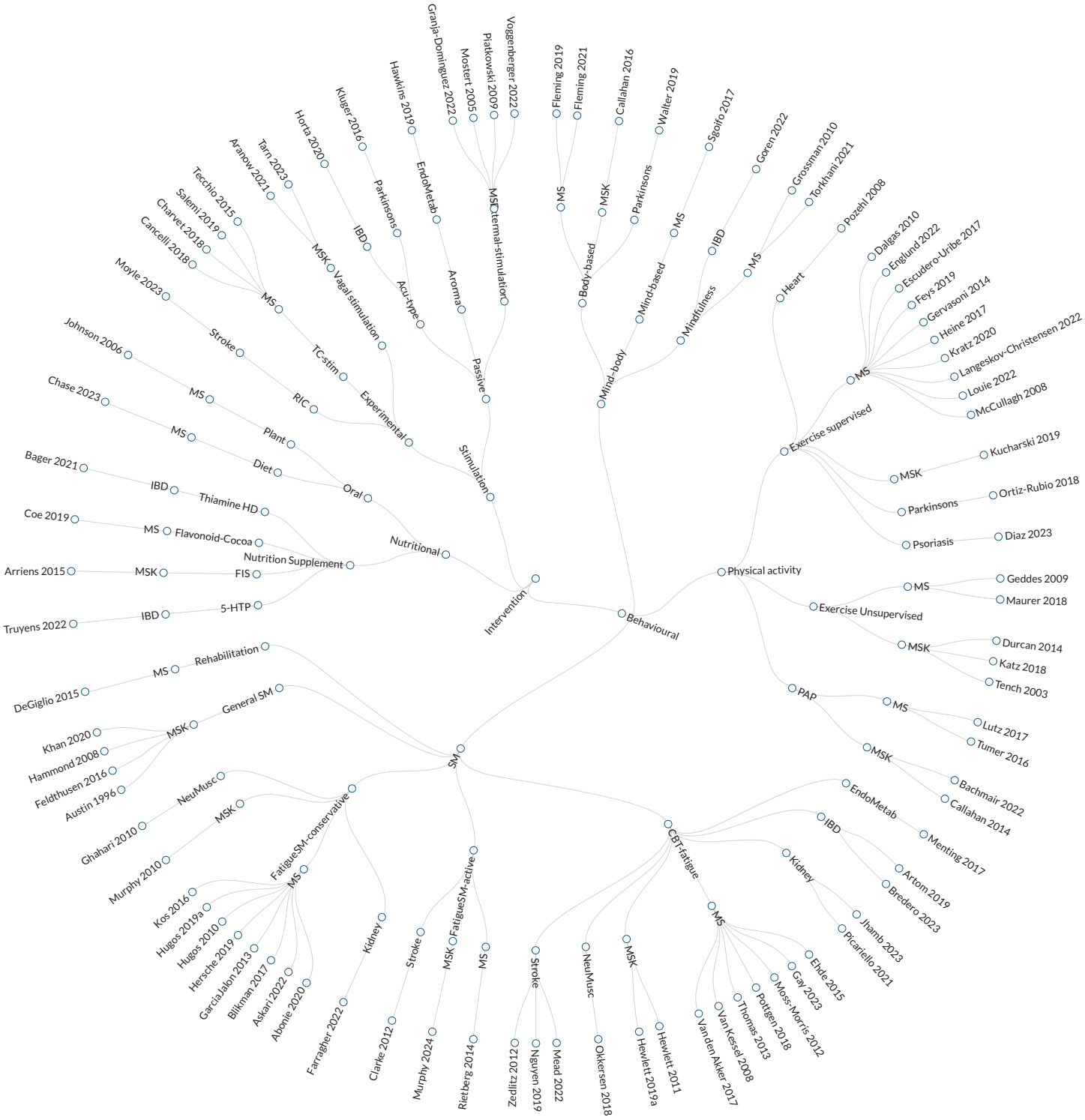


**FIGURE 6** Radial network of interventions grouped by condition. RIC, remote ischaemic conditioning.

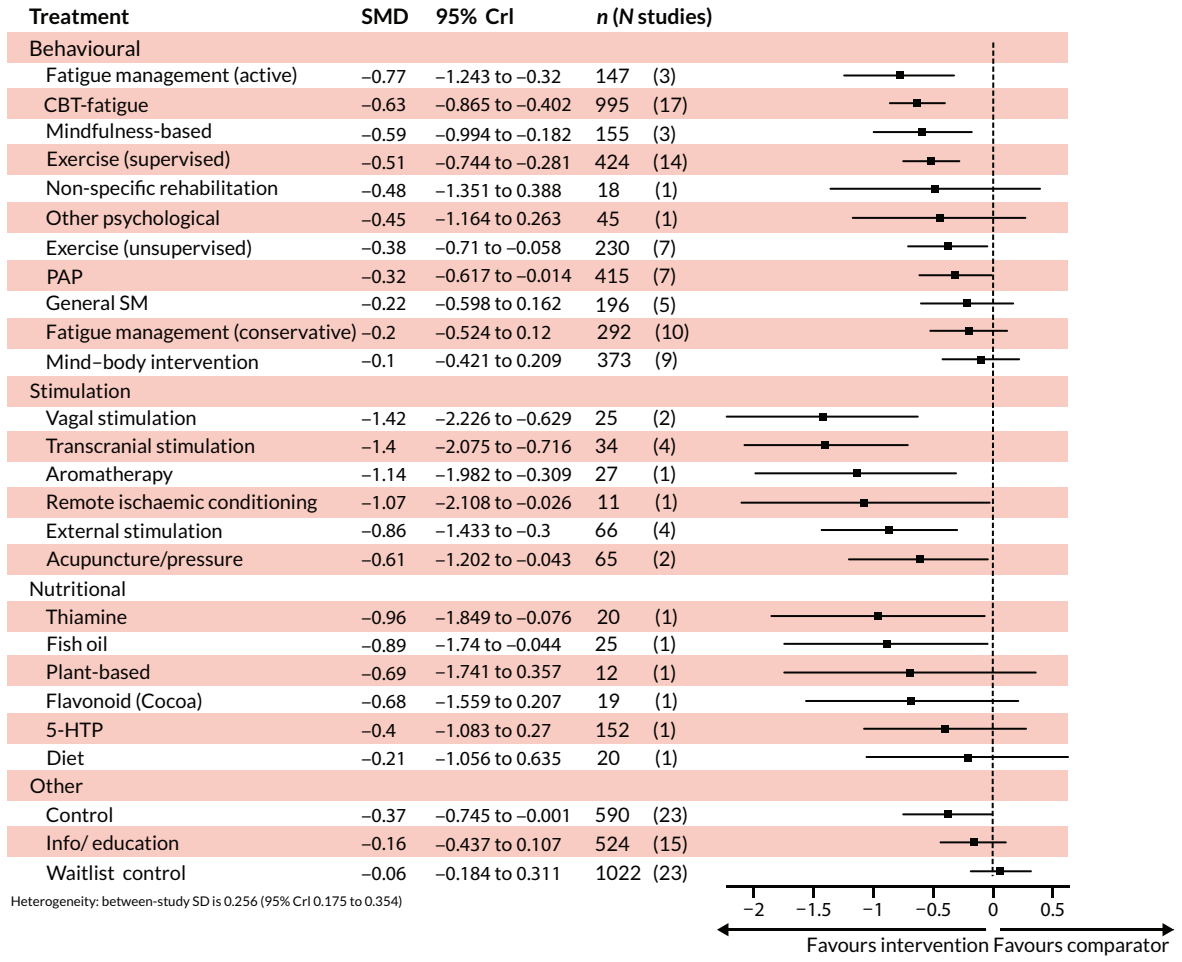


**FIGURE 7** Predicted effects on fatigue outcomes at end of treatment. Note: fatigue outcomes of interventions reported relative to UC, at end of treatment, with 95% CrI. The number of participants (*n*) and the number of studies (*N* studies) are given for context. Broad intervention categorisation is also presented to aid interpretation (behavioural, stimulation, nutritional and other). The 'control' node is displayed as this functioned to ensure connectivity of the network, but this is not an active intervention for consideration/recommendation. SD, standard deviation. Reproduced with permission from Leaviss *et al.*[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY-ND 4.0) license, which permits others to copy and redistribute the material in any medium or format for any purpose, even commercially, provided the original work is properly cited. If you remix, transform, or build upon the material, you may not distribute the modified material. See: https://creativecommons.org/licenses/by-nd/4.0/deed.en. The figure above includes minor additions and formatting changes.

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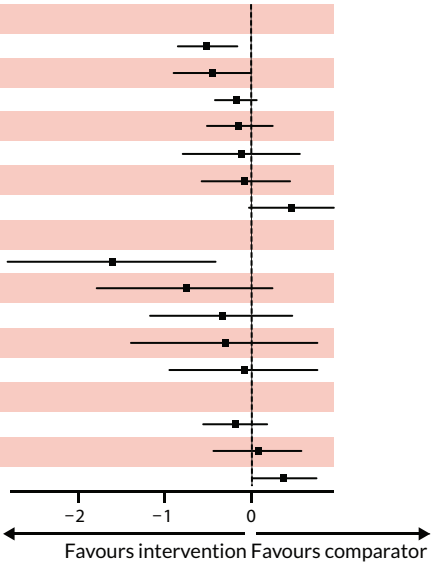
**(a) Short term (up to 3 months after end of treatment)**

| Treatment | SMD | 95% CrI | *n* (*N* studies) | |
|---|---|---|---|---|
| Behavioural | | | | |
| PAP | −0.51 | −0.844 to −0.171 | 121 | (1) |
| Exercise (supervised) | −0.44 | −0.888 to 0.003 | 48 | (3) |
| CBT-fatigue | −0.17 | −0.415 to 0.062 | 467 | (7) |
| Fatigue management (conservative) | −0.13 | −0.508 to 0.246 | 243 | (7) |
| Fatigue management (active) | −0.11 | −0.789 to 0.544 | 32 | (2) |
| General SM | −0.08 | −0.568 to 0.434 | 116 | (2) |
| Mind–body intervention | −0.46 | −0.038 to 0.946 | 51 | (2) |
| Stimulation | | | | |
| Vagal stimulation | −1.59 | −2.803 to −0.409 | 12 | (1) |
| Remote ischaemic conditioning | −0.76 | −1.78 to 0.241 | 11 | (1) |
| External stimulation | −0.34 | −1.155 to 0.463 | 22 | (1) |
| Transcranial stimulation | −0.3 | −1.384 to 0.763 | 9 | (1) |
| Acupuncture/ pressure | −0.08 | −0.949 to 0.751 | 18 | (1) |
| Other | | | | |
| Info/ education | −0.19 | −0.553 to 0.174 | 145 | (6) |
| Control | 0.08 | −0.436 to 0.567 | 137 | (7) |
| Waitlist control | 0.37 | 0 to 0.752 | 153 | (3) |

Heterogeneity: between-study SD is 0.079 (95% CrI 0.004 to 0.308)




**(b) Long term (more to 3 months after end of treatment)**

| Treatment | SMD | 95% CrI | *n* (*N* studies) | |
|---|---|---|---|---|
| Behavioural | | | | |
| Mindfulness-based | −0.54 | −0.99 to −0.105 | 76 | (1) |
| PAP | −0.52 | −0.862 to −0.184 | 159 | (2) |
| General SM | −0.42 | −0.919 to 0.099 | 231 | (3) |
| Fatigue management (conservative) | −0.42 | −0.9 to 0.087 | 175 | (3) |
| Exercise (supervised) | −0.41 | −0.913 to 0.086 | 79 | (2) |
| CBT-fatigue | −0.4 | −0.627 to −0.214 | 640 | (9) |
| Mind–body intervention | −0.03 | −0.53 to 0.472 | 60 | (2) |
| Other psychological | 0.05 | −0.525 to 0.602 | 45 | (1) |
| Stimulation | | | | |
| Remote ischaemic conditioning | −1.26 | −2.261 to −0.264 | 11 | (1) |
| Other | | | | |
| Control | −0.5 | −0.971 to −0.051 | 104 | (3) |
| Info/ education | −0.26 | −0.642 to 0.156 | 229 | (4) |
| Waitlist control | 0.05 | −0.697 to 0.808 | 34 | (1) |

Heterogeneity: between-study SD is 0.096 (95% CrI 0.005 to 0.356)

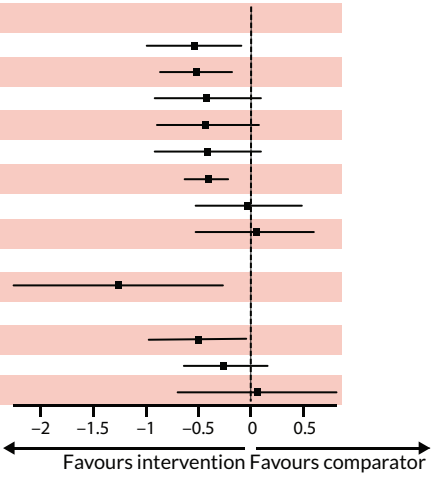



**FIGURE 8** Predicted effects on fatigue outcomes at short- and long-term follow-up. Note: outcomes reported to UC, at (a) short-term analysis and (b) long-term follow-up with 95% CrIs. The number of participants (*n*) and the number of studies (*N* studies) are given for context. The 'control' node is displayed as this functioned to ensure connectivity of the network, but this is not an active intervention for consideration/recommendation. SD, standard deviation. Reproduced with permission from Leaviss *et al.*[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY-ND 4.0) license, which permits others to copy and redistribute the material in any medium or format for any purpose, even commercially, provided the original work is properly cited. If you remix, transform, or build upon the material, you may not distribute the modified material. See: https://creativecommons.org/licenses/by-nd/4.0/deed.en. The figure above includes minor additions and formatting changes.