Effectiveness of Interventions For Fatigue in Long-term conditions (EIFFEL): Protocol

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Contents

1 Background and rationale

1.1 The problem

Persistent fatigue is common in long-term medical conditions, particularly when multiple conditions are present [1]. Alongside tiredness, it includes a sense of needing to rest, or of difficulty in initiating or sustaining voluntary effort [2 3]. People with medical conditions describe their fatigue as "more than ordinary tiredness" [4] with impacts that go beyond the symptom itself [5 6]. Fatigue is invisible: people's experience of fatigue is often not taken seriously by clinicians [7]. We will conduct an evidence synthesis of the clinical and cost-effectiveness of non-pharmacological interventions for fatigue in medical conditions, with a particular emphasis on the feasibility and acceptability of these to patients.

While fatigue is common in medical conditions, its presence correlates poorly with disease severity [8-11] and it often persists after the disease has been brought under control [12]. Fatigue appears to be a transdiagnostic phenomenon with similarities in experience and impairment across different conditions [7]. Current models of fatigue include biological [13] and psychosocial factors [1 9], with increasing interest in the role of altered signalling between the brain and body [14-17]. There are currently no licensed drug treatments for fatigue in long-term conditions.

Non-pharmacological interventions have been developed to overcome fatigue in medical conditions. These include interventions focusing on physical activity (either increasing or managing activity), psychological therapies, and body-mind interventions (including yoga, tai-chi etc). In practice, many fatigue rehabilitation and self-management programmes contain multiple components. Some also aim for wider targets (e.g. general wellbeing). People with fatigue have complex needs [18] including reduced symptoms, having their experience of fatigue validated [19] and returning to meaningful activities [20].

As fatigue is increasingly understood in terms of processes in the body, brain, and signalling between the two [14 16 17], the different types of non-pharmacological interventions described above are scientifically plausible. However, to many patients with fatigue this rationale is often not apparent. Thus, proposed interventions may be seen as illogical (physical exercise when they are already exhausted), stigmatising (psychological interventions implying fatigue is "all in the mind" and can be overcome just by thinking differently) or inappropriate (body-mind interventions being too "alternative"). These conceptual barriers to engagement with interventions are an important aspect of this problem [21].

2 Aims and objectives

2.1 Aim

The overall aim of the review is 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 review includes a nested qualitative focus group study to obtain information from people with lived experience of fatigue in longterm conditions which will be used to guide decisions within the evidence synthesis.

2.2 Objectives

- Conduct a quantitative evidence synthesis focusing on effectiveness, cost-effectiveness and acceptability

- Conduct a qualitative evidence synthesis focusing on acceptability
- Conduct a series of focus groups with people with lived experience of fatigue in long-term conditions which is inclusive of diverse medical conditions and diverse populations and communities and use material from the focus groups to guide the evidence synthesis
- Integrate the quantitative and qualitative syntheses to provide accessible and clear summaries of our findings, with practical information to support clinical decisions and service design
- To review the outputs of the evidence synthesis and interpret it for policy, practice and future research
- Produce recommendations for further research
- 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.

3 Evidence Synthesis

We will combine quantitative and qualitative evidence synthesis techniques.

3.1 Health technologies being assessed

The review will examine non-pharmacological interventions and strategies for fatigue in long-term medical conditions. For this review, we define strategies as things that people with long-term conditions do to manage their fatigue and interventions as programmes which teach or support the use of strategies. We will focus on evaluations of interventions (whether patients allocated to a programme of X had benefit) rather than strategies (whether patients who did Y felt it improved their fatigue). The scope of interventions will be as follows.

3.1.1 Interventions

A wide range of non-pharmacological interventions will be in scope for this review, shown in table 1 below. This table is provisional and will be reviewed (a) in the first round of PPI focus groups (b) during the search and extraction process. The table includes individual components, which can be present on their own or in combination with other components, and pre-specified combinations. Where there are sufficient studies to categorise with a higher level of detail (e.g. different types of physical exercise or body mind intervention) we will consider this. The table also includes interventions with combinations of components. We will differentiate between combination interventions which include only one or two elements (such as cognitive behavioural therapy) and more mixed interventions with elements of many components but not specific focus.

Table 1 Proposed intervention categories

Category	Defining features	Examples / sub-categories
Individual components		
Physical Exercise	Focus on participation without incremental targets	Aerobic, resistance, natural environment
Graded exercise	Focus on exercise with incremental targets	Graded Exercise Therapy

Activity regulation	Evaluating and adapting activity to maximise value from current capacity	Activity pacing, managing the "energy envelope"
Body mind	Focus on awareness of and conscious changes to bodily states	Yoga, Tai-chi, acupuncture
Cognitive	Focus on thoughts about the body / activity	Cognitive component of CBT
Emotion regulation	Focus on modifying exposure or responses to stress / negative emotion	relaxation, visualisation, counselling, mindfulness
Technology assisted	Use of sensors / other devices to provide feedback or guide activity	Activity tracking, virtual reality
Nutritional supplements	Dietary supplements, traditional medicines	Co-enzyme Q, evening primrose.
Sleep	Structured approach to sleep management	CBTI
Education	Written or taught information about fatigue and its management	
Pre-specified Combinations		
CBT	Cognitive + Exercise / Graded Exercise, may include "homework"	
Mixed rehabilitation	Multiple components from above	

3.1.2 Medical conditions

Any long-term medical condition not specifically excluded (see below) will be included in the scope of this review. We will define the term "long term conditions" according to the NHS definition of "an illness that cannot be cured but that can usually be controlled with medicines or other treatments". We will not set limits on medical conditions within this other than those specified in the below section 'excluded conditions'. We will include studies of interventions for fatigue in mental illnesses that fall within this definition and for which the NHS incentivises formal annual long-term condition reviews (such as schizophrenia and bipolar disorder) but not studies in common mental disorders such as depression and anxiety which - while they can be chronic - are more often intermittent. However, we recognise that depression and anxiety are common comorbidities in long term conditions and can adversely affect fatigue. Where a study of intervention for fatigue in a long term condition includes information about patients with depression or anxiety, we will still include them in the analysis and we will extract information about any effect of depression or anxiety on the outcome where it is reported.

3.1.3 Excluded medical conditions

We will exclude studies where the primary focus is cancer, long-COVID, post-viral fatigue, ME/CFS, conditions resulting from accidents or injuries, and developmental disorders. We will also exclude disorders characterised by persistent physical symptoms which are disproportionate to currently recognised pathology and are sometimes known as "medically not yet explained" even when clearly defined symptom criteria exist (e.g. fibromyalgia or irritable bowel syndrome).

3.1.4 Preferred outcomes

We will prioritise outcomes which specifically measure fatigue; however we will include as secondary outcomes measures of quality of life and which look at uptake and engagement with interventions. We will also include functional impairment and return to work as secondary outcomes. We will separate outcome into short term / end of treatment (<=13 weeks from enrolment or <=6 weeks from expected end of treatment) and medium/long-term (>13 weeks from enrolment and >6 weeks from expected end).

3.1.5 Framework for analysing and reporting findings

We will integrate findings from the quantitative and qualitative elements of our work using the Joanna Briggs Institute FAME (Feasibility, Appropriateness, Meaningfulness and Effectiveness) model [22] as follows.

- *Feasibility* : the extent to which an activity or intervention is practical or viable in a context or situation – including cost-effectiveness.
- *Appropriateness:* the extent to which an intervention or activity fits with a context or situation.
- *Meaningfulness:* refers to how an intervention or activity is experienced by an individual or group and the meanings they ascribe to that experience.
- *Effectiveness:* the extent to which an intervention achieves the intended result or outcome. Based on these criteria we will use the JBI grading of evidence[23] as either strong or weak as follows

Strong recommendation

- it is clear that desirable effects outweigh undesirable effects of the strategy
- there is evidence of adequate quality supporting its use.
- there is a benefit or no impact on resource use, and
- values, preferences and the patient experience have been taken into account.

Weak recommendation

- Desirable effects appear to outweigh undesirable effects of the strategy, although this is not as clear
- There is evidence supporting its use, although this may not be of high quality
- There is a benefit, no impact or minimal impact on resource use,
- Values, preferences and the patient experience may or may not have been taken into account.

3.1.6 Contextual and implementation factors (acting as “barriers & facilitators”)

From extensive experience of qualitative evidence synthesis we recognise that generation of lists of barriers and facilitators as a 'menu' of the most important barriers and facilitators, which interventions can be designed to overcome or amplify, can be overly simplistic [24]. In the context of complex interventions this approach ignores the interdependence of various factors operating within complex social systems [25]. It also fails to consider the potential unintended consequences of interventions that operate within such complexity. Our approach will be nuanced, considering data from qualitative studies as a potential source for understanding how the extent to which certain factors operate (or do not operate) in specific contexts determines the feasibility, acceptability and effectiveness of specific interventions. Our approach will therefore be informed by realist principles but not governed by them. A mixed methods synthesis combining and integrating results from the quantitative review of effectiveness with findings from the qualitative evidence synthesis of acceptability will offer a credible alternative to realist methodology. [26]

3.2 Search strategy – quantitative synthesis

3.2.1 Principles

We will conduct a comprehensive search of bibliographic databases, combining terms for fatigue and long-term conditions (we will use generic terms and derive specific lists). Search strategies will include free-text and thesaurus terms (where available). Terms will be combined using Boolean Operators and database-specific syntax. Searches will be limited to English Language and studies conducted with adults (18+ years) only. Methodological search filters will identify systematic reviews and RCTs.

3.2.2 Databases

We will search MEDLINE & MEDLINE-In-Process; EMBASE; CINAHL; PsycINFO; The Cochrane Library; Science & Social Sciences Citation Indexes via Web of Science. Databases will be searched from 1990. Search alerts and tracking of key citations will be put in place and will provide monthly updates such that study identification will be updated up until the beginning of the economic evaluation (June 2024).

3.2.3 Additional search methods

We will check reference lists of identified reviews and included trials for further relevant references. We will use citation searching to identify relevant cited references and additional studies by key authors.

3.2.4 Inclusion criteria

We will include randomised controlled trials as the sole eligible study design and use the PICOS (Population, Intervention, Comparator, Outcomes, Setting) framework to specify the inclusion criteria.

*3.2.4.1 **P**opulation*

Adults (18 years +) with one or with multiple long-term physical and/or mental health condition. Studies of populations with multiple conditions will be included. We will exclude cancer, long-COVID, post-viral fatigue, medically not yet explained conditions, and acute conditions resulting from accidents or injuries, and developmental disorders.

*3.2.4.2 **I**ntervention*

Non-pharmacological fatigue management interventions. Only studies of interventions where a stated explicit aim is to manage fatigue will be included. Any non-pharmacological intervention or strategy will be eligible (see Table 1). Interventions with multiple components meeting the above criteria will be included, even where one component is pharmacological.

Interventions may be face-to-face or delivered at a distance and may include technology-assisted interventions. Individual and group interventions, and different forms of delivery of otherwise similar interventions will be treated as separate interventions in the first instance.

*3.2.4.3 **C**omparator*

“Usual care”, another non-pharmacological intervention or attentional control. We will not include trials which solely compare drug with non-drug treatments.

*3.2.4.4 **O**utcomes*

Primary outcomes – fatigue as measured by a validated instrument. Secondary outcomes - uptake of intervention; acceptability; persistence/adherence; attrition; adverse events; quality of life; functional impairment; return to work.

*3.2.4.5 **S**etting*

Primary, secondary, or tertiary care, or community-based settings.

3.2.5 Additional inclusion criteria for cost-effectiveness studies

The cost effectiveness review will include published economic evaluations. It will use the same PICOS framework as the effectiveness review with the additional restriction to study settings in the UK NHS.

To be included in the economic analyses studies must report both costs and benefits measured in terms of quality-adjusted life-years (QALYs). Studies will be included based if they report costs using either a societal perspective or an NHS and personal social services (PSS) perspective.

3.3 Search strategy – qualitative synthesis

3.3.1 Principles

We will adapt the search methods used for the quantitative review but with a focus on qualitative research and process evaluations of clinical trials. We will follow Cochrane EPOC principles of purposive sampling of studies for inclusion, aiming for a spread of conditions and interventions and to favour theory-informed papers over 'thin' descriptive accounts [27]. We will purposively favour UK, English-speaking and EU countries in order to collect data with the greatest relevance to NHS services.

We will use a comprehensive search combining free-text and thesaurus terms for long-term conditions and fatigue with methodological search filters, optimised for sensitivity and specificity, to identify qualitative research and mixed methods or qualitative process evaluations. We will maximise the interpretive value of included studies by only including those that focus on fatigue in either the title or the research question.

3.3.2 Databases

We will search MEDLINE & MEDLINE-In-Process; EMBASE; CINAHL; PsycINFO; The Scopus; Science & Social Sciences Citation Indexes via Web of Science. Databases will be searched from inception. Search alerts will be set up in order to retrieve newly published studies. These will run monthly for the first 12 months of the project.

Additional search methods

We will check reference lists of identified reviews and any included studies for further relevant references. We will use The Citation Chaser [28] to identify cited and citing references. Search guidance that we have authored for Cochrane [29] also privileges identification of doctoral theses and book chapters, mainly identified through CLUSTER searching techniques [30].

3.3.3 Inclusion criteria

We will use the PICoS (**P**erspective, phenomenon of **I**nterest, **C**ontext, **S**tudy design) framework to define inclusion criteria.

3.3.3.1 Perspective:

Adults (18 years +) with one or with multiple long-term condition.

3.3.3.2 Phenomenon of Interest

Fatigue, privileging the impact of any intervention on prior fatigue but also including day-to-day concerns about managing fatigue and its wider impact, with or without intervention management strategies. Only studies with a specific focus on fatigue will be included, as indicated by title or research question.

3.3.3.3 Context

Any context, whether primary, secondary or tertiary care, or community-based settings.

3.3.3.4 Study Design

Qualitative research or qualitative and mixed methods process evaluations.

3.4 Review methods – quantitative synthesis

3.4.1 Study selection and data extraction for effectiveness

We will use a two-stage sifting process for inclusion of studies, (title/abstract then full paper sift). Titles and abstracts will be scrutinised by two assessors according to pre-specified inclusion and exclusion criteria. Full paper checking for inclusion will be conducted by one reviewer and checked by another. Disagreements will be resolved between the two reviewers by discussion, or if needed in consultation with the clinical experts. All studies fulfilling the inclusion criteria will be retrieved.

Data will be extracted by one reviewer and checked by a second reviewer using a form developed specifically for the current review. Data will focus on condition and intervention characteristics, study size and both primary and secondary outcomes. Study identification and data extraction for the cost-effectiveness review will be performed by a single reviewer. We will assess the quality of studies using the Cochrane Risk of Bias 2 tool [31].

3.4.2 Extraction of intervention components

We anticipate the proposed review will include complex interventions. Whilst definitions of the meaning of 'complex interventions' vary [32], we will consider complexity of interventions to include an interaction not only between individual properties of interventions, but also the interdependence between intervention components and the systems within which they are implemented. Data will therefore be extracted to reflect sources of complexity such as: the use of multiple components; the expertise and skills of those delivering and receiving the intervention; and the intervention context including settings.

We will consider components to be individual elements of an intervention that have the potential to causally influence outcomes. We will extract data relating to individual components of interventions. As described previously, we will code interventions by type. An intervention may consist of a single component e.g. exercise in the natural environment, or it may consist of multiple components, e.g. exercises, meditation, and education. Where an intervention has multiple components, the study will be coded into each of the individual components, as well as being coded as a 'multi-component' intervention. We will not know the full range of interventions until the list of included studies is final, however we anticipate components such those listed in Table 1.

We will structure our data extraction of the included interventions around the 'Template for Intervention Description and Replication statement' (TIDieR)[33]. Prior research [34] has shown that less than 40% of studies reporting non-pharmacological interventions provide adequate descriptions of the interventions, and due to this anticipated paucity of data we will extract intervention details using the 6-item TIDieR-Lite [35].

3.4.3 Aggregation of evidence across multiple or similar conditions and interventions

We recognise that decisions about which conditions or interventions should be viewed as sufficiently similar to permit aggregation of evidence across conditions ("lumping or splitting") have implications for both the strength of findings and their interpretation. We also recognise that people with long term conditions may have differing views from professionals about this, with consequences for both the conduct and findings of research[36].

To ensure the representation of the views of people with lived experience of fatigue in multiple Longterm conditions, we will carry out a nested qualitative PPI focus group study. This is described in Section 4.

Decisions about which conditions and interventions to aggregate / disaggregate in the synthesis will be informed by three factors.

- The summarised preferences / recommendations from the lived experience focus groups
- A set of prior umbrella categories provided by the research team in the original application: *"four categories as follows: (1) Neurological, including Multiple Sclerosis, Stroke and Parkinson's Disease; (2) Peripheral conditions including heart failure, chronic lung disease and osteoarthritis; (3) Inflammatory, including inflammatory bowel, joint or connective tissue disease; and (4) metabolic, including chronic kidney disease and transplantation."*
- Evidence arising from the meta-regression (see section 3.4.4)

Final decisions about the synthesis will be will be formed We will test the validity of these groupings further and, if necessary, revise the classification based on input from our clinical experts, our PPI panels, and any relevant identified literature during the early development stages of the work. The rationale for decision-making outcomes will be made transparent in the final outputs.

3.4.4 Analysis and synthesis of effectiveness

Extracted quantitative data will be scrutinised, and a decision regarding the feasibility of conducting an NMA will depend on statistical evaluation for inconsistency, which will be performed if there are feedback loops in the network. Conceptual evaluation for transitivity will be performed by comparing the potential treatment effect modifiers across included studies.

We will follow Cochrane Collaboration guidelines for meta-analyses [37] and will draw on our experience of analysing reviews in related fields with high levels of heterogeneity in the data [38]. Where there is sufficient data to create a meaningful network of comparisons between interventions, we will perform a component network meta-analysis for the primary outcome fatigue, which will allow us to explore the efficacy of complex interventions with different components and combinations of components.[39]

It is anticipated that different studies may have used different scales to measure fatigue, we will use the standardised mean difference as the measurement for the treatment effect. Both additive main effect model and full interaction model will be explored. Parameters will be estimated in a Bayesian framework. Where there is sufficient sample data, conventional reference prior distributions will used. In the case of there being relatively few studies, an informative prior distribution will be assumed for the between-study standard deviation [40]. In the case of moderate to large heterogeneity, we will perform a meta-regression analysis based on conditions and sociodemographic data to explain any heterogeneity in treatment effects between studies where compatible data allow.[41]

All analyses will be conducted in the freely available software packages WinBUGS [42] and R using the R2WinBUGS interface package.[43] Convergence to the target posterior distributions will be assessed using the Gelman-Rubin statistic.[44] The absolute goodness of fit will be checked by comparing the total residual deviance to the total number of data points included in an analysis. The relative goodness of fit comparing the additive main effect model and full interaction model will be checked by comparing the Deviance Information Criterion (DIC).[45]

Results will be presented using the posterior median treatment effects, 95% credible intervals (CrI) and 95% prediction intervals (PrI). The 95% PrI indicates the extent of between study heterogeneity by illustrating the range of SMDs that might be expected in a future study.

For the acceptability data, we will perform a standard random effect network meta-analysis where there is sufficient data to form a meaningful network.[46] Where there is insufficient data to construct a meaningful network for outcomes of interest, we will use random effects meta-analysis to generate pairwise comparisons. In the case that no evidence can be synthesised, we will use narrative synthesis to summarise the results of these studies.

3.4.5 Analysis and synthesis of cost-effectiveness

This comprises two parts: a systematic review of published cost-effectiveness studies and an additional de novo economic assessment (described in section 3.6).

The analysis and synthesis of economic evaluations will be conducted by a single reviewer. The costing perspective for each study will be described and any sensitivity analyses using a narrower or broader perspective will be reported where available. A narrative review will summarise cost-effectiveness results, study applicability and study limitations using the checklist applied in NICE guidelines[47].

Cost-consequence studies which provide an estimate of the incremental cost of delivering fatigue management interventions in a UK setting will be set aside and used to inform the de novo economic assessment where possible.

3.4.6 Extraction of acceptability data from quantitative studies

During the data extraction phase of the analysis of effectiveness we will also extract the following data (where provided): Participation rates (vs eligible invitation rate); participant characteristics; adherence to intervention (e.g. sessions attended); and attrition from the study.

3.4.7 Extraction of sociodemographic data from quantitative studies

For each study we will extract information about the socio-economic and ethnic backgrounds of participants in addition to age and gender. We will examine the effects of this data in two ways: first by using meta-regression, and secondly by examining context specific mechanisms in the qualitative analysis.

3.5 Review methods – qualitative synthesis

3.5.1 Study selection and data extraction

We will use two-stage sifting as described for the quantitative studies. All qualitative studies fulfilling the inclusion criteria will be retrieved. We will extract data on study characteristics together with verbatim comments from participants and/or author observations, thereby focusing on authenticity and significance. We will assess the quality of studies using the Cochrane EPOC tool for qualitative research within a qualitative synthesis, based on the CASP checklist.

3.5.2 Analysis and synthesis of qualitative research

In selecting methods for synthesis we will follow the Cochrane Collaboration guidelines for qualitative evidence synthesis which we co-authored[48]. If we can identify a robust and credible framework that integrates well with the quantitative studies, we will use framework synthesis. Alternatively, in the absence of a framework, we will use thematic synthesis. Our team is equally familiar with either method. We will map sibling qualitative research and

process evaluation studies to their associated trials, thus controlling for contextual variation[25]. We will formally document reflexivity for the members of the qualitative review team.

3.6 De novo economic assessment

In addition to the review, we will conduct a de novo economic assessment to explore the potential cost-effectiveness of non-pharmacological fatigue management interventions identified in the clinical effectiveness review. This takes three steps: estimating quality of life gain from interventions, estimating cost of delivering interventions and assessing cost-effectiveness. Inclusion of societal costs will be explored if these are provided in the costs provided by published analyses, but otherwise the costing perspective for this analysis will be NHS and personal social services. Future costs and benefits occurring beyond 1 year will be discounted at 3.5% per annum.

3.6.1 Estimating QOL gain from interventions

Where data allow, we will use published mapping algorithms to estimate EQ-5D utility values (or utility values from a suitable alternative preference-based utility measure) from the fatigue outcomes estimated by the evidence synthesis for each cluster of interventions over which effectiveness estimates have been pooled. Suitable mapping algorithms will be identified initially from the HERC database [49]. If this does not identify a suitable method of estimating EQ-5D from the fatigue outcomes reported in the clinical studies, then a targeted review of mapping algorithms will be conducted focused on the outcomes included in the evidence synthesis and preference-based measures of quality of life such as the EQ-5D and the SF-6D.

We will then use an area under the curve approach to estimate the QALY gains for the time period over which fatigue outcomes are reported (medium/long term if data available and short term / end of treatment otherwise). From this we will estimate the net monetary benefit of the QALY gains by assuming that a QALY is valued at £20,000. This net monetary benefit is the maximum cost for the intervention that would allow it to be cost-effective under the typical threshold applied by NICE

3.6.2 Estimating costs of delivering interventions

We will estimate the range of costs required to deliver the interventions included within each cluster for the evidence synthesis. This will be informed by published estimates of the costs from cost-effectiveness or cost-consequence studies identified in the economic review where these data are available. Where these are lacking, information on the resource use required to deliver the intervention, such as time and personnel, will be combined with PSSRU unit costs to estimate the intervention cost per patient. Non-intervention costs such as changes in usage of primary or secondary care or medication usage following intervention will only be included where these are already included in an estimate of costs provided by a published analysis [50]. Similarly, societal costs such as productivity costs or travel costs will only be included where these are already included in an estimate of costs provided by a published analysis.

3.6.3 Assessing cost-effectiveness

Finally, we will assess whether the non-pharmacological fatigue management interventions identified in the review have potential to be cost-effective by comparing the estimated range of costs required to deliver the interventions to the maximum cost which is determined by the net monetary benefit provided by the QALY gain. This will be used to inform research recommendations by identifying non-pharmacological fatigue management interventions that

have the potential to be cost-effective that would warrant further investigation within a future economic evaluation.

We anticipate that very few of the published clinical studies will have an accompanying within-trial economic evaluation, hence, whilst we plan to review and summarise any published economic analyses that we find, including any head-to-head comparisons of cost-effectiveness, our main task is likely to be the de novo evaluation. The aim of the de novo economic evaluation is to explore the potential cost-effectiveness of non-pharmacological fatigue management interventions identified in the clinical effectiveness review and identify the interventions that would warrant further investigation in future cost-effectiveness studies.

The de novo analysis will not be undertaken on a study by study basis. Instead we will focus on clusters of interventions that have been considered sufficiently similar to be analysed together within the network meta-analyses. For each cluster of interventions we will use the outcomes from the NMA to estimate an expected QALY gain. We will then estimate the range of intervention costs for the interventions included within each cluster. We will then use a net benefit approach to assess the maximum intervention cost that is justified by the QALY gain and compare this with the range of intervention costs to assess if interventions of this type have the potential to be cost-effective. This method will allow us to conclude if none, all or only the lowest cost interventions with the cluster have the potential to be cost-effective, given the range of costs required to deliver them and our assumption that they provide similar benefits.

There may be some clusters of interventions where the clinical evidence from the NMA suggests that effectiveness is poor or very uncertain and other clusters of interventions with stronger evidence. In which case, we may choose to focus the de novo economic analysis on those interventions with the strongest evidence for clinical effectiveness as these are likely to have the highest potential to be cost-effective.

The assessment of clinical outcomes will be over a standardised timeframe as the NMA will group outcomes according to whether they are short or long term. We will make assumptions regarding the time points used in the area under the curve calculator of the QALY based on the most commonly reported time points for short and long-term outcomes in the studies contributing to the NMA. The sensitivity of the analysis to these assumptions will be tested in scenario analysis using the longest and shortest time points reported in any contributing study.

The decision as to whether to provide head-to-head cost-effectiveness comparisons will be dependent on the network of studies available for the condition or set of conditions included in a single NMA. We hope that the network will allow us to provide a comparison for each cluster of interventions against a single ‘usual care’ comparator. Providing this information is anticipated to be more easily interpretable by clinicians and other researchers than lots of different head-to-head comparisons, as comparison against a common comparator will highlight which interventions have the potential to be cost-effective and should therefore be the focus of future research. This is our aim in the de novo analysis rather than a precise estimate of cost-effectiveness for every single intervention based on individual studies.
Integration of review findings

3.6.4 Overview

Methods for integrating quantitative and qualitative evidence are recognised as relatively immature. However, we will use current state of the art methods to integrate this diverse evidence including use of matrices and an overarching logic model [51]. The logic model will

be used to map evidence to factors regardless of whether it is derived from quantitative data or qualitative data.

3.6.5 FAME GRADE

Evidence from quantitative and qualitative reviews will be mapped to the domains of the FAME framework. Although the collective contribution of these reviews will largely be complementary (i.e. interventions depend upon acceptability for their effectiveness) we will particularly attempt to identify contradictions or discrepancies (e.g. to explore when acceptable interventions have not been shown to be effective or where aspects of interventions have been found to be unacceptable to their target audiences). This analysis will be used to generate priorities for adaptation or for further evaluation.

Where possible we will use combined GRADE/GRADE-CERQual Summary of Findings Tables that accommodate assessments for confidence in both quantitative and qualitative findings.

3.6.6 Sociodemographic characteristics, contextual and implementation factors ("Barriers and facilitators"),

We will use both the quantitative and qualitative analyses, and their integrated findings to report on the relationship between sociodemographic characteristics and engagement with or benefit from interventions. We will explore whether there are systematic reasons for under-representation of particular groups in research or differences in outcomes. Rather than producing a list of barriers or facilitators we will produce a logic model describing factors which may influence uptake and outcomes and their apparent interactions.

3.7 Contingencies

3.7.1 Analytical power and pooling of conditions / interventions

We anticipate that for most condition-intervention pairs there will be insufficient high-quality evidence to produce strong recommendations. We will thus explore pooling data across conditions and interventions to increase the power of our findings. We will ensure that patient views influence these decisions through our PPI work and will analyse and report the logics that patients describe in articulating these views.

3.7.2 Acceptability

We anticipate relatively few studies that formally assess acceptability of interventions to patients. We will therefore triangulate findings of quantitative extractions of acceptability with the results of our qualitative review and PPI groups. We will frame our results using the Joanna Briggs Institute FAME (Feasibility, Appropriateness, Meaningfulness & Effectiveness) model [22] in order to address the different facets of acceptability.

3.7.3 Sparsity of data in qualitative evaluations of trials

In the event of few rich within-trial qualitative evaluations where the focus is fatigue, we will extend our searches and analysis to include (a) within-trial qualitative evaluations of similar interventions but with less focus on fatigue (i.e. fatigue management may not be the primary aim of the intervention, however fatigue is included as an outcome) and/ or (b) qualitative descriptions of interventions in non-trial studies of the lived experience of fatigue in medical conditions.

4 Focus Groups

4.1 Aim

The specific aim of this qualitative study is to answer the research question “How do people with fatigue in long-term medical conditions view the nature of fatigue and appropriateness of non-pharmacological interventions across different conditions?”

4.2 Objectives

4.3 Overview

We will recruit 6 focus groups designed to reflect diversity of participants, clinical conditions, and location. Each group will meet on three occasions during the study: twice near the start, and once towards the end.

Participants will attend focus groups, based on either their condition type, or socio-economic or ethnic background. For example, there may be one focus group of patients with MS, and another focus group of South-Asian females experiencing fatigue from a variety of conditions. The focus groups may be online using video conferencing software, or in a meeting space at the University or a community location, depending on needs and preferences of attendees. Online groups will be used to increase geographical diversity and provide more equitable access for those with difficulty travelling to a focus group. Face to face groups will be used to increase equity for those in underserved groups by meeting with them in their own space and reducing the consequences of digital poverty.

We will conduct the focus groups using participatory approaches that we have found effective in PPI work with diverse patient groups, including using concise information summaries to inform interactive discussion and activities such as preference sorting. Focus groups will be recorded and transcribed for reporting.

4.3.1 Equality Diversity and Inclusion

We will attend to equality, diversity, and inclusion in group composition by specifically holding at least two of the groups with underserved population groups through the South Yorkshire Deep End Research Alliance. We will ensure that the focus groups hear the experiences of individuals living in areas of high socio-economic deprivation – in whom long-term conditions are more common and for whom the burden of treatment is often greatest - and of people from non-white ethnic groups whose experience of accessing healthcare may be different from that of white British citizens. We will evidence this diversity by collecting and reporting data relating to EDI in our outputs. The lead for PPI within the investigator team currently works in the Deep End Research Alliance and has extensive experience of PPI with diverse groups and of research into persistent symptoms

4.3.2 Support for participants

The PPI team (academic lead and lived experience investigators) will offer pre and post meeting support to ensure that participants are comfortable within meetings and supported to share their views fully. We will provide remuneration in line with current NIHR guidance. In particular we will arrange for payments rather than vouchers for participants as our default. Due to the long time period between first round and second round focus groups, we will provide all participants with a bi-monthly project update in the form of a newsletter, and an opportunity for an online meet if wanted.

4.3.3 Flexibility of participation

In order that focus groups have between 4 & 8 participants in each meeting (we regard 6 as a maximum for online and 8 for in-person) we will recruit and invite more participants than this to the preparatory group meetings. This will allow participants who are unable to attend the first round groups to take part in the second round ones (and vice versa).

4.4 Participants and recruitment

4.4.1 Inclusion criteria

- Adults, aged 18 years or older.
- Experiencing a long-term medical condition (including inflammatory conditions, and diseases of cardiac, respiratory or central nervous system) which is stable, with or without current disease modifying or symptomatic treatment.
- Experiencing fatigue in relation to one or more long-term medical conditions to an extent that it interferes with normal activities of daily living on several days most weeks either currently or for a sustained period in the past few years.

4.4.2 Exclusion criteria

4.4.3 Conditions specifically excluded in the research commissioning brief by the funder

- Cancer
- Medical conditions reliant on fatigue for diagnosis (e.g. fibromyalgia, ME/Chronic Fatigue Syndrome).
- Conditions arising from infection (long covid, other post-viral illness) or injury

Other

- Lack capacity to consent to take part in study.

4.4.4 Identification of participants

We will use multiple approaches to ensure a diverse sample. Specifically, this will involve (1) contacting patients through specialist clinics (2) recruitment through patient organisations (3) recruitment through PPI networks.

4.4.4.1 Medical conditions through specialist clinics.

Clinicians working in medical specialties such as neurology, gastroenterology, rheumatology and renal medicine at Sheffield Teaching Hospitals (STH) will invite patients from their clinics or services. These patients may already be members of an existing PPI group. In addition members of the research team will invite known members of PPI groups linked to their own organisations. Invited individuals will be sent an information pack about the study either by post or by email. The information pack will contain a patient information sheet and a response form in two formats: on paper and as a link to an online response form (Google Forms) hosted by the University of Sheffield. Additionally, the invitation will contain a study phone number for queries before completing the form. The response forms will include simple demographics (Age, gender, ethnicity); relevant medical conditions and availability to take part either face to face or online. The forms will include space for contact details (both email and phone with the opportunity to state a preference). On completion of the form, individuals will receive a “holding” email thanking them for expressing an interest and indicating that they will be notified about further invitation.

4.4.4.2 Medical conditions through patient organisations.

We will approach patient organisations for medical conditions in which fatigue is common, including multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis and kidney disease. We will ask them to sent out information about the study with a response email and phone number for expressions of interest. Individuals who express an interest will then be sent an information pack by post including the patient information sheet and response form (including online link) as described above. On completion of the form, individuals will receive a "holding" email thanking them for expressing an interest and indicating that they will be notified about further invitation.

4.4.4.3 Identification through community-based research involvement networks

We will approach community/voluntary organisations, including those specifically related to conditions in our inclusion criteria or fatigue in general, and other organisation serving communities in areas of socio-economic deprivation, or ethnic minority communities. Many of these will already be known to the PPI team, and some we will have worked in partnership with previously.

We will ask them to send out information about the study with a response email and phone number for expressions of interest. Individuals who express an interest will then be sent an information pack by post including the patient information sheet. As these groups have experience of recruiting participants to research in a range of ways, we will offer the group a choice between individual members contacting the research team or one person making contact with the team on the group's behalf. Where this is the case we will collect basic demographic information (as described above) at the start of focus groups.

4.4.4.4 Data management of response forms

Data from the online response forms will be stored on a University of Sheffield server. Data will be used to purposively short-list individuals for invitation to take part in focus groups. These individuals will be contacted by a member of the research team using their preferred contact method. The remaining individuals will be sent an email explaining that we have more people expressing an interest than we need but we wish to hold their details for 15 months in case we need further focus group members later on. In addition, we will create anonymised summaries of the expression of interest data to enable us to report on diversity at each stage of the process.

4.4.5 Invitation, enrolment and consent

Individuals who have been shortlisted for participation in focus groups will be contacted by a member of the research team to discuss the study and answer any questions. Consent will be taken, in advance of the focus group beginning either by return of a completed digital consent form by email (either format) or signed paper consent form (face to face).

4.5 Focus Groups

Consent will be re-confirmed verbally at the beginning of the focus group. Focus groups will follow a topic guide which may be modified prior to data collection with PPI input and will be adapted as focus groups progress in order to reflect emerging findings and to confirm / disconfirm ideas as they arise. Focus groups will last approximately 90 minutes, with a 10 minute break. Focus groups will be facilitated by one of our expert by experience co-applicants, supported by the academic lead the qualitative work.

All focus groups will be audio-recorded (using either an encrypted digital recorder or using Google Meet meeting recording). In addition to this the supporting facilitator will take notes

and photographs (not of participants) to record the sorting exercises, and discussion around specific interventions.

4.5.1 Focus group content

4.5.1.1 Meeting 1 - Preparatory group meeting – framing the study

From our initial PPI work we have recognised that fatigue is a hidden disability and frequently a contested issue. The nature of this study means it is thus vital to ensure that the research team are transparent about their own perspectives. Our experience is that it is also important to give participants space to describe their personal experiences of fatigue and to recognise that. While this is not the primary focus of the PPI, we regard it as an essential prelude to focusing on the research itself – by ensuring participants know they are being heard and also building a sense of group cohesion .

The first round of focus group meetings will have three objectives: (1) ensuring people are comfortable with the environment / technology being used (2) giving space for participants to share their own experiences of fatigue; (3) introducing the materials to be discussed at the subsequent two rounds of focus groups and the methods within the groups.

4.5.1.2 Meeting 2 – Exploring fatigue across conditions to inform research decisions.

The second round of focus group meetings will take place 1-3 months after the first round. Their aim will be to elicit views about similarities and differences in the experience of fatigue – and interventions for it - across different conditions. Specifically, they will focus on (i) similarities and differences between different diseases / contexts in relation to fatigue; (ii) similarities and differences between different non-pharmacological interventions for fatigue; (iii) aspects of interventions from a patient perspective which need to be captured in the research in order to support informed choices. In particular, there will be questions about aggregating evidence across conditions and interventions to inform the data management and analysis strategies for the concurrent evidence synthesis. Facilitators (including one or both of our experts by experience) will present lay friendly descriptions of interventions, and systematically work with the groups to see which they feel belong together. We will use sorting activities to achieve this, encouraging participants to “think-aloud” as they do them. Facilitators will be briefed to expect that focus groups will attach different degrees of importance to components of interventions, which may challenge researchers’ assumptions. Findings from this round of focus groups will be rapidly collated and shared with the whole research team in order to inform aggregation of conditions / interventions and other relevant strategies.

4.5.1.3 Meeting 3 – interpreting the findings

The third focus groups meetings will take place in months 12-18. They will primarily be to elicit views about the emerging findings from the research. Specifically, they will focus on (i) how people with lived experience of fatigue understand and interpret the analysis of effectiveness; (ii) how they understand and interpret the qualitative analysis; (iii) their views on proposed dissemination materials. As groups take place at different points in this stage of the research process, the balance between the three components will vary depending of the timing of a particular meeting.

These groups will examine the results of the evidence synthesis using the FAME GRADE scheme [24]. They will inform the conclusions of the evidence synthesis and the content and design of output materials. As for the second round of meetings, lay summaries of studies

and interventions will be provided, and the panels encouraged to comment on their perceptions of interventions, particularly around feasibility, appropriateness, and meaningfulness. This will involve a range of participatory approaches. The diverse nature of the groups will provide a wider context to study findings.

4.6 Analysis

The aim of the analysis of rounds 1 and 2 of the focus groups will be to identify patient preferences for the approaches to be used in the evidence synthesis and to understand the logics behind those preferences. To achieve this, we will use thematic analysis informed by phenomenology. The qualitative academic lead will undertake analysis with support from the experts by experience and the PI. The analysis will be iterative, to allow for changes to be made to the topic guide as we progress through the focus groups, to enable us to further explore areas of importance.

The findings from the sorting activities which will be in note and picture form will be collated and summarised, to reflect both agreement and differences within and between groups.

The aim of the analysis of round 3 of the focus group will be to understand how patients view and interpret the findings of the evidence synthesis. It will use framework analysis to collate information about feasibility, appropriateness and meaningfulness of interventions presented, while also allowing for new themes to emerge. The qualitative academic lead will undertake analysis with support from the experts by experience and the PI.

4.7 Data , handling and record keeping

The focus group recordings will be transcribed and simultaneously anonymised of any identifying data (both participants and third parties). These transcripts will then be saved in a separate file on secure university servers. Transcripts, notes and images will be managed and analysed within the NVivo research data environment

During the consent process, participants will be given an explanation of how the data collected in the study will be processed, and an undertaking that the data gathered in the study will not be reported, discussed or made available in such a way that will enable them to be identified. Paper consent forms will be scanned, the file transferred to secure University servers, and the paper copy destroyed. All data will be stored securely on secure University servers throughout the research period and for seven years once the study is completed.

Only basic personal information relevant to carrying out the study will be collected. Personal details will be stored in a separate password protected folder and will only be accessible by those who the principal investigator has delegated responsibility to (and who accept the duties of confidentiality created in the project). The study identification code or key that links the data collected to the personal details of the participants will be kept securely in a password protected file and separately from the data. Personal details will not be stored on the same devices used to collect the study data.

The identifying professional or organisation and the research team will have access to participant's personal data as required to carry out the study - i.e. contact details and basic demographic information. Participants will be informed about this in the information sheet. This data may be made available to regulatory authorities (or in the case of NHS identification, the NHS trust) where it is required. Transmission of data will only occur over secure (encrypted) connections.

Participants will be asked to consent to the data (de-identified transcripts) being made available, on request, for subsequent analysis. Any such analysis would require ethical approval by the University of Sheffield.

Each participant will be given a unique identifier. When we publish our results or give presentations, we will use this identifier to refer to participants. We will never use or reveal the participant's real name or any data that can identify him/ her. This will be clearly stated in the participant information sheet. However, videos cannot be made anonymous. We will only use videos outside the research team if the participant has given us permission to do so on the consent form.

In terms of confidentiality, the participants will be given an explanation of how the data will be processed, and an undertaking that the data gathered in the study will not be reported, discussed or made available in such a way that will enable them to be identified.

5 Ethical issues and Safeguarding

This research study will not offer any particular benefit for those who partake.

5.1.1 Safeguarding participants

A flexible research process has been designed in order to safeguard participants from physical or psychological harm, for example, the option of online or in person focus group. The research team will prioritise the needs of participants, with the help of our experts by experience. This includes consideration about the length of focus groups, and the need for breaks.

As our participants are people who are experiencing fatigue as part of a long-term condition, there is a risk of the research process exacerbating their fatigue. This risk will be mitigated by ensuring fully informed consent and emphasising the right to withdraw from part of all of the research process at any point.

Discussion of long-term conditions and fatigue may cause psychological distress. If a participant becomes emotionally distressed during any aspect of the research, the researcher will check that they have informal support available, and if not, signpost to more formal support (e.g. voluntary organisations).

5.1.2 Safeguarding of research team

The interviews may include distressing narratives - for example descriptions of stigmatisation - and therefore there is a risk that exposure to this could be upsetting for the facilitator. In order to minimise this, we will provide adequate training for the research including trial runs of focus groups. As the research team includes people with lived experience, we will meet regularly and there will be opportunity for regular debriefs.

5.1.3 Safeguarding policy & contacts

We will follow the University of Sheffield's Preventing Harm in Research and Innovation (Safeguarding) Policy - https://www.sheffield.ac.uk/research-services/ethics-integrity/safeguarding/about. This policy stipulates that a member of the research team carries out the role of ‘designated safeguarding contact’. The designated safeguarding contact will be the study PI Professor Chris Burton. This contact has the responsibility of recording any safeguarding incidents and ensuring proper procedures are followed. Before the research commences all members of the research team will be trained in the appropriate routes for reporting safeguarding concerns or incidents, and an action plan for handling and escalating these. Incidents or concerns will be handled by the researchers by gathering as

much information as possible from the individual who has raised the concern. This will be done in a sensitive manner, providing support to the individual, whilst ensuring the safeguarding process is clearly outlined to them using appropriate language. This information will then be shared with the designated safeguarding contact and pertinent procedures followed in line with the host organisation policy. In some cases, it may be necessary to inform the participant's GP or make an immediate referral to the crisis team. If the concerns refer to people other than the individual, social services and/or the Police may need to be informed.

6 Study Management

The qualitative academic lead will project manage this study, with the support of the Principal Investigator. Team meetings with the expert by experience co-applicants will be held on a regular basis to discuss recruitment, any issues raised during the focus groups, and to review the analysis and dissemination. Representatives from the team will also attend management meetings of the whole study, and report of progress of the focus groups.

6.1.1 Changes to the protocol

If it is necessary for the protocol to be amended, the amendment and/or a new version of the study protocol will be notified to or approved by the ethics committee. If new information becomes available that may affect participants' contribution or safety on the study, revised participant information sheets will be prepared and approved by the ethics committee before participants are provided with this new information and asked to re-consent.

6.1.2 Monitoring

The project will be subject to internal monitoring by a researcher within the University group to ensure quality of data. Monitoring/ audit will consist of activities such as source data verification and review of investigator site file essential documents, informed consent procedures, inclusion and exclusion criteria, focus group schedules, source data consistency and safety documentation and reporting to ensure compliance with legislation. The project will be conducted to Good Clinical Practice (GCP) standards. All of the research team will have appropriate GCP training.

7 Study oversight committee

The funder will, in coordination with the research team, constitute a study oversight committee which will meet on three occasions during the study to review the protocol, progress of research and evolving findings. This will include review of decisions about aggregating / disaggregating data from similar conditions and interventions (see section 3.4.3).

8 Role of the funder

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