Protocol (V4.1)

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INTRODUCTION

This is the protocol for the production of an evidence map focussed on research studies related to myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) and presenting these with reference to the James Lind Alliance Priority Setting Partnership (JLA PSP) priority questions[1]. The goal is to produce a robust evidence map, with involvement of key stakeholders, which can inform decisions about future research relating to ME/CFS.

This protocol is written following the Campbell Evidence and Gap Map Guidance[2] and reported following the PRISMA-ScR checklist[3] (see Appendix 1). This protocol incorporates plans for stakeholder involvement in this review.

Title

ME / CFS: an evidence map of research studies and how these address key themes in the JLA PSP research priorities

Background

Myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) is a chronic neurological disease[4], with fluctuating symptoms affecting multiple body systems, including nervous and immune systems. ME/CFS affects around 250,000 people in the UK and 17 million people worldwide; with an estimated minimum prevalence of 0.2% of the UK population[5]. ME/CFS is characterised by debilitating fatigue (physical and/or mental exhaustion) that is worsened by activity, post-exertional malaise (a disproportionate worsening of symptoms following even minor physical or mental exertion) and several other common symptoms including

pain, unrefreshing sleep, cognitive impairment, gastrointestinal problems, and orthostatic intolerance[5-8]. ME/CFS has a substantial health burden, negatively impacting ability to function and quality of life[9-11]. ME/CFS affects people of all ages and genders, but most people with ME/CFS are female, and people who are older are more likely to be more severely affected[8].

ME/CFS is a poorly understood condition[12]. In 2022, multiple stakeholders (including people with ME/CFS, their families, carers and health professionals) worked in partnership to reach consensus on research priorities for ME/CFS[1]. The resulting top 10+ research questions comprise a series of broad, overlapping questions focused on the biomedical cause, diagnosis and treatment of ME/CFS[1]. To support and encourage future informed, high quality, useful collaborative research and research funding, worldwide, a comprehensive map of existing research evidence (and evidence gaps) is essential[13].

Synthesis of research evidence relating to ME/CFS is recognised to be challenging due to the use of a wide range of diverse case definitions and diagnostic criteria[5]. Historically, clinical labels have lacked consistency, including ME, CFS, CFS/ME, chronic fatigue, fatigue syndrome and other terms. Further, diagnostic criteria have varied leading to inconsistencies in patient groups within studies. Diagnostic criteria in which post-exertional malaise (PEM, sometimes referred to as post-exertional symptom exacerbation) is a core component include: CCC (Canadian Consensus Criteria 2003)[14], ICC (International Consensus Criteria 2011)(this is an update of the CCC criteria)[15], IOM (Institute of Medicine 2015)[16] and NICE 2021[12]. Other diagnostic criteria in which PEM is not a core component include: Oxford[17] and Fukuda (Centers for Disease Control)[18] criteria. A comprehensive map of existing research evidence, including all research regardless of clinical terms and diagnostic criteria, will bring together studies which include varied populations of patients. Consequently, it is essential that the diagnostic criteria used in studies are central to mapping of this evidence.

AIM

We will produce an evidence map. An evidence map summarises what evidence is available; it does not summarise what the evidence says[2].

Objective: To produce an evidence map of national and international research in ME/CFS, taking into account diagnostic criteria, and showing how current research maps against key themes covered by the JLA PSP research priorities[1].

Review questions:

- What is the volume (number of studies and participants), and key characteristics (including study design, population, and focus/theme), of research in this field?
- Which key themes have research evidence which has (and has not) included participants with different diagnostic criteria?
- Which of the PSP research priority topics have/have not been addressed by research evidence? Where do evidence gaps remain?

METHODS

Inclusion criteria

In line with the broad nature of our proposed evidence map, we define the inclusion criteria using the Population-Concept-Context (PCC) framework (rather than the Population-Intervention-Comparison-Outcome (PICO) framework, which focusses on maps of evidence of effectiveness of interventions).

Population: people with diagnosed ME/CFS*, of any age (i.e. including both children, 0-18 years, and adults > 18 years).
*We will include studies based on the authors' definition of ME/CFS. This will include studies in which any diagnostic criteria are used (e.g. CCC, ICC, IOM, NICE 2021, Oxford, or Fukuda criteria). We will also include studies which do not report diagnostic criteria but, where we judge that the population could be people with ME/CFS (see further detail in Exclusion criteria, below). We will include studies in which participants self-report that they have ME/CFS. We will include studies in which the population is described using any of the following terms:

- ME/CFS, ME, CFS, CFS/ME, or similar terms (e.g. fatigue syndrome)
- Chronic fatigue or similar terms, where this is the primary diagnosis and is not related to another diagnosed health condition, or reason (see Exclusion criteria below)

We will include studies which include a mixed population (i.e. people with a range of different conditions) where this specifically includes ME/CFS, and the number of people with ME/CFS are reported (and is ≥ 10 people).

However, we will subsequently categorise all included studies according to the diagnostic criteria used within the study (see Data coding). Our rationale for this is that our aim is to identify all research evidence in this field; including any research where the authors report that participants had ME/CFS and then categorising according to the diagnostic criteria used, is a pragmatic approach which will enable comprehensive mapping of research in this field. Further, this inclusive approach will avoid the exclusion of important studies which, due to their study design, rely on self-reported diagnosis (e.g. The DecodeME Study includes participants "*who self-reported a diagnosis of ME, CFS, ME/CFS or CFS/ME by a health professional*"[8]), However, the diagnostic criteria used in studies will be a core element of our evidence map, enabling stakeholders to explore the research evidence in relation to the diagnostic criteria used during the selection of study participants (see Evidence Map section for further details).

Concept: Any research relating to ME/CFS. In line with the scope of NIHR, we will include any translational, clinical or applied health research, and will exclude studies involving animals or animal tissue. We will include all research studies with ≥ 10 human participants with ME/CFS that seek to address a question relating to the cause, diagnosis, treatment, management or impact of ME/CFS.

Context: We will include studies regardless of context, i.e. we will include studies from any geographical location, any healthcare setting, and relating to any aspect of ME/CFS including (but not limited to) risk factor association (including biological mechanisms), diagnostic

assessment, treatment/management, natural history/prognosis. Our rationale for not placing any limitation on context is that we are aiming to compile a broad map of all research relating to ME/CFS; context will be considered within our data extraction and mapping.

Study designs: We will include quantitative and qualitative research studies, systematic reviews, and economic evaluations. We will include studies focused on the development and/or testing of an instrument or tool to measure outcomes in people with ME/CFS where data from a cohort of people with ME/CFS are reported. This excludes audits, quality improvement projects, commentaries, opinion pieces and case studies/series with < 10 participants with ME/CFS. We will also exclude reviews which do not meet criteria for being a 'systematic' review'*. Our rationale for including any type of research study is that we are aiming to produce a broad map of all research in this field. Our rationale for excluding studies with < 10 participants is that very small studies and single case reports are unlikely to provide substantive useful information which can inform future research. We are excluding audits, quality improvement projects, commentaries and opinion pieces as these are not research studies and therefore not relevant to our aim of bringing together research studies.

* We define a 'systematic review' as: *a research process in which literature relevant to a stated question is identified and brought together (synthesised) using explicit methods[19], including reporting of inclusion/exclusion criteria, search methods and details of included studies*. We will include systematic reviews regardless of the type of evidence synthesised (i.e. quantitative, qualitative, mixed-methods) and the type of question addressed (e.g. epidemiology, intervention effectiveness, diagnostic test accuracy, patient experiences).

<u>Exclusion criteria</u>

We will exclude studies in which the specified population is people with fatigue explicitly related to another health condition (e.g. cancer-related fatigue, stroke-related fatigue) or pharmaceutical adverse reactions.

We will exclude studies in which the population is people with work / occupation-related fatigue.

We will exclude studies in which the specified population is people with*:

- Gulf war syndrome
- Functional somatic disorders
- Fibromyalgia
- Postural Orthostatic Tension Syndrome (POTS)
- Long COVID
- Epstein Barr Virus
- Broad groups of rheumatic disorders or auto-immune conditions

unless these studies include an identified subset of people with ME/CFS and meet our inclusion criteria.

We will exclude studies:

- With < 10 participants with ME/CFS.
- With mixed populations of patients (including ME/CFS) if the numbers of included participants with ME/CFS are not specifically reported.
- In which the participants are carers of people with ME/CFS (e.g. studies focussed on carer burden).

*Note: this list is not comprehensive of all conditions/diseases that will be excluded (unless there are a subset of people with ME/CFS that meet our inclusion criteria). Rather this list provides examples of conditions/diseases that we anticipate will be identified from our search, which could potentially include subsets of people with ME/CFS. During the selection process, reviewers will meet regularly to discuss the application of the criteria (including discussion of studies where there are disagreements between two independent reviewers). Notes of any additional conditions/diseases, or scenarios, and the selection decisions related to these, will be kept, aimed at further clarification of these criteria and increased agreement between reviewers within further full text assessments.

Searching and screening

Search strategy: We will search the following databases:

- the Cochrane Central Register of Controlled Trials (CENTRAL) via Cochrane Register of Studies Online (CRSO)
- MEDLINE (Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE
- Embase via Ovid
- CINAHL via Ebsco

Searches will be restricted by date starting from 1 January 2018 to 29 May 2023 and by language to English only. No filters will be used for study type, so that all publication types will be retrieved. The MEDLINE search strategy is included in Appendix 2; this will be adapted for other listed databases.

Search dates: due to the potentially large volume of evidence in this field, we propose a pragmatic approach by initially searching for a 5-year period (i.e. 2018-2023). We will reflect on this process during the course of the review and - if considered necessary - extend the search period. Where appropriate, we will seek the views of stakeholders relating to whether there would be benefits to extending the search for systematic reviews of specific topics if none have been identified. These views will be used to inform research team decision making. We will transparently document decisions and our rationale for these. Our rationale is that we do not want to contribute to research waste by duplicating previously conducted evidence syntheses; by including systematic reviews we should ensure that all relevant research is captured. Further, adopting a pragmatic approach to searching can ensure completion of a timely scoping review, maximising available time and efficiency.

Language: we will only include studies published in English. This is due to the limited time and resources available for this evidence map, meaning we are unable to retrieve and translate studies published in languages other than English.

Management of searching and screening: Results of the search will be de-duplicated in Endnote and uploaded into Covidence. Two reviewers will independently apply inclusion criteria to titles and abstracts, deciding if each is an 'exclude' or 'potential include'. Any studies where there are disagreements between independent reviewers will be discussed by two (different) reviewers who will reach consensus on a decision.

Full texts will be obtained for all studies considered as 'potential includes'. Two reviewers will independently apply inclusion criteria, and consensus reached through discussion between two (different) reviewers for any papers where there are disagreements. All full-text papers selected as 'include' at this stage will be included in the review. We will include at the study level (i.e. if there are multiple papers reporting the same study, we will group these together and count as a single study).

Reasons for exclusion will be documented as one of: 1. Published before 2018; 2. Wrong study design; 3. Wrong patient population; 4. Less than 10 participants with ME/CFS; 5. Other. Where there are multiple reasons for exclusion, we will adopt a hierarchical approach, selecting the first appropriate reason for exclusion from the list above. Where reviewers are uncertain (i.e. cannot reach consensus through discussion between reviews) about whether a study does or does not meet the inclusion criteria, key stakeholders may be consulted and these views used to inform research team decisions.

The results of the search will be reported, including a PRISMA flow chart[3] which clearly details the decision processes at each stage of the process.

Data coding

Within Covidence, two reviewers will independently extract/code the following data from included studies, with disagreements resolved through discussion:

- Author, year
- Publication type – coded as:
    - Full text paper
    - Abstract
    - Other
- Country in which study was conducted
- Aim – verbatim text[a]
- Study design – coded as:
    - Systematic review[b]
    - Randomised trial
    - Non-randomised studies (includes non-randomised trial, controlled before & after study, interrupted time series study, repeated measures study)[20]
    - Cohort study (prospective / retrospective)
    - Case-control study
    - Survey / cross-sectional study
    - Case series (≥ 10 participants)
    - Qualitative (includes interviews, focus groups, ethnographic studies)
    - Mixed methods study

    - Economic evaluation
    - Not specified
    - Other
- Population – coded as (selecting all that apply):
    - Children and young people (up to age 18 years)
    - Adults
    - Older adults (> 65 years)
    - Not specified
    - Other
- Sample size – total number of participants with ME/CFS (and number of included studies for systematic reviews (the number focussed on ME/CFS where a review includes mixed populations))
- Definition of / diagnostic criteria for ME/CFS used within study:
    - CCC[14]
    - ICC[15]
    - IOM[16]
    - NICE 2021[12]
    - Oxford Criteria[17]
    - Fukuda (Centers for Disease Control) criteria[18]
    - Other (specify)
    - Not specified
- Severity of ME/CFS within people recruited to the study, as reported by study authors, includes:
    - Mild
    - Moderate
    - Severe
    - Very severe
    - Not specified
- Theme (see Appendix 3):
    - Risk factor association (including biological mechanisms)
    - Diagnostic assessment
    - Treatment / management
    - Natural history / prognosis
    - Other
- Gender/sex. Are results presented separately for people who are:
    - Men
    - Women
    - Other gender
- Race/ethnicity. Are results presented separately for people who are:
    - Aboriginal / First Nations
    - Arab
    - Asian (not specified)
    - Black
    - East Asian
    - Hispanic/Latinx
    - Jewish

- Mixed
- Not specified
- Pacific Islander
- South Asian
- White
- Other (please specify)

[a] For studies where the primary focus in not on ME/CFS no further data coding will be conducted, and these studies will be reported separately (i.e. not within the Evidence Map).
[b] Systematic reviews will be coded accordingly to their eligibility criteria (rather than according to their included studies). However, we will note the number of included studies and the number of participants (with ME/CFS) within these included studies and include this information within the evidence map.

Piloting: We will pilot our coding form with at least 30 included studies. We will discuss the results of the pilot coding and refine accordingly. We will document any revisions to categories and justification for these.

Additional coding: following the dual data extraction and coding within Covidence, we will export data into Excel and will apply a series of post-hoc codes. These will include:

- Country in which study conducted – coded by geographical region and income using the World-Bank database.
- Themes and subthemes - We will add subthemes using an iterative approach, building on those proposed in Appendix 3, as required. This will be developed in consultation with key stakeholders. This approach will aid consistent decision-making, ensuring similar studies can be considered at the same time and that new subthemes are applied to all studies. Further, this approach will enable volume of studies to be considered when making decisions about the need for additional subgroups.

Quality assessment of included studies

Systematic reviews: We will assess the risk of bias of included systematic reviews using AMSTAR 2 (a critical appraisal tool for systematic reviews)[21]. Our justification for this is that knowledge of the quality of systematic reviews will be central to informing decisions about future research and to judgement of certainty in the findings of these systematic reviews. Two independent reviewers will make AMSTAR judgements, with disagreements resolved through discussion. We will document areas of disagreement and iteratively develop notes to support consistent responses. If necessary, we will consult with key stakeholders in order to inform our decision. Within our evidence synthesis, we will note that the AMSTAR tool provides a judgement of the quality of methods of the systematic review, and not the studies included within the systematic review.

Primary research: We will not assess risk of bias of primary research studies. Rationale for this is that evidence maps often do not involve conducting quality appraisals of studies, due to the workload of this. Instead, as recommended, we will code and filter according to study design[2]. Our justification for this is that by capturing the study design we will be able to

provide a sense of the type of work that is currently being conducted, informing decisions about future systematic reviews and/or primary research.

Evidence map

Following consultation with our stakeholders, we will generate a test/pilot map. We will get feedback on this test/pilot map from our stakeholders and consider modifying it accordingly.

Following Campbell guidance, we will aim for an evidence map which has a maximum of 25 row and columns (4-6 categories, each with up to 5 subcategories)[2].

We will produce an interactive evidence map using EPPI-mapper[22]. The primary constructs of interest reflected within the map will include (i) themes/subthemes (reflecting the JLA PSP research priorities), (ii) study designs and study size, (iii) ME/CFS diagnostic criteria used within study, (iv) whether the study is focussed on adults (or older adults) only, children/young people only, or a mixed population. One possible structure is drafted below, but this will be discussed with the stakeholders and refined accordingly.

		Risk factor association				Diagnostic assessment	Natural history / prognosis			Treatment / management
		Biological mechanisms	Immune system factors	Infection	etc		Recovery patterns	Different types	etc	
Systematic review										
Study design	Cohort	*								
	Case-control									
	Cross-sectional									
	Etc									

* 'bubbles' in the cells would indicate if studies included adults, children, or mixed populations. Alternatively, the bubbles in the evidence map could be created to show studies according to diagnostic criteria employed in each study. Clicking on the bubbles would take the user to a reference list, listing the relevant studies (and abstracts/DOI if available). As another alternative, the diagnostic criteria could be reflected as rows. These decisions will be informed through stakeholder involvement.

SYNTHESIS

We will write a brief narrative synthesis summarising the volume (number and size of studies) and key characteristics (e.g. study design, country, population) of the research evidence relating to key areas of ME/CFS (according to the themes and subthemes that have been identified, and with the addition of new subthemes that have arisen from the identified studies). The narrative will report the volume of studies which have used different diagnostic criteria. The synthesis will provide a commentary on the characteristics of the people included in the studies, with reference to severity of ME/CFS, gender and ethnicity. This commentary will not bring together the results of the identified studies.

We will include a document which defines all key terms used within the map, including definitions of all the themes and subthemes. This will be co-produced with our stakeholders.

TEAM REFLEXIVITY / POSITIONALITY STATEMENT

To enhance transparency, our narrative synthesis will include a team reflexivity statement summarising the different goals of the researchers working on the evidence map. We will

employ the definition of reflexivity as "a set of continuous, collaborative, and multi-faceted practices through which researchers self-consciously critique, appraise, and evaluate how their subjectivity and context influence the research processes"[23].

DISSEMINATION / KNOWLEDGE MOBILISATION

We will develop and maintain a knowledge mobilisation plan. We will discuss this with our stakeholders and refine iteratively through the course of the project. A key aim of this plan will be to engage with and communicate the findings of this evidence map with researchers and research funders. This aim includes trying to communicate with researchers who are not currently actively working in the ME/CFS field but who may be in a position to conduct research which addresses key evidence gaps.

We will work with our stakeholders to explore how we can support wider knowledge mobilisation and measure longer-term impact. It should be noted that the input from NESSIE (supported by NIHR) only continues until December 2023, so it will be important to identify mechanisms and strategies - and lead people - to maintain and measure longer term impact.

TIMELINE

	April 2023	May 2023	June 2023	July 2023	Aug 2023	Sept 2023	Oct 2023	Nov 2023	Dec 2023
Development proposal									
Protocol			1		2				
Stakeholder involvement	3		4	5	6		7, 8		
Search and screening									
Data coding									
Quality assessment systematic reviews									
Evidence map							9		
Synthesis									
Knowledge mobilisation								10	11
Review management									

[1] Protocol submitted to NIHR for sign-off by 27th June 2023
[2] Protocol finalised by 10th August 2023
[3] Stakeholder meeting 17 April 2023
[4] Stakeholder meeting 13 June 2023
[5] Stakeholder meeting – 18th July 2023, 1-2pm
[6] Stakeholder meeting – 15th August 2023, 2-3pm

[7] Stakeholder meeting – 3rd October 2023, 12-1pm
[8] Stakeholder meeting – 24th October 2023, 1-2 pm
[9] Evidence map completed by 31st October 2023
[10] Journal paper submitted by 30th November 2023* (*extension to NIHR 2-week timeframe to enable feedback from people living with ME/CFS)
[11] Final knowledge mobilisation products produced/disseminated by 15th December 2023* (*as above, extended timeframe to enable feedback from people living with ME/CFS)

STAKEHOLDER ENGAGEMENT

A NESSIE PPI co-investigator will oversee the stakeholder involvement in this review. We will follow national standards and principles[24-26], and we will consider the lessons related to accessibility produced by the ME/CFS JLA PSP (Document drawn up by C Dransfield, Action for ME, with additional comments from PSP steering group members, 20/4/22) and the draft document on 'how to enhance your ME research by involving people with ME as patient advisors and participants' (S Tyson, University of Manchester, 7 June 2023).
We will develop and implement a stakeholder engagement plan. We will gather feedback and advice from stakeholders, which we will use to inform decisions about the development of the evidence map. The aim of stakeholder engagement will be to ensure that the evidence map is useful and usable to stakeholders. We will report the involvement of stakeholders using the ACTIVE framework and GRIPP2 reporting checkist (short form)[27, 28]

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NESSIE TEAM

Alex Todhunter-Brown, Jackie Price, Sheila Cameron, Pauline Campbell, Emma France, Rosie Hill, Catriona Keerie, Sarah Markham, Peter Matthews, Gillian Mead, Aileen Neilson, Gerry Stansby, Marlene Stewart, Evropi Theodoratou, Cathryn Broderick, Julie Cowie, Bridget Davis, Candida Fenton, Ceri Sellers, Katie Thomson.

CONTRIBUTIONS OF AUTHORS

Please see Appendix 4 for the CRediT author statement.

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APPENDIX 1: Reporting checklist for this protocol

We have used the checklist for Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR)[3], as (while this is a protocol for an Evidence Map and not a scoping review) this is the most appropriate checklist. We note, and justify, where our reported item differs from the item within PRISMA-ScR:

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	Identified as an Evidence Map, Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	Not applicable (this is a protocol)
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	Introduction & background (Page 1-2) justify conduct of an evidence map.
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	Page 2, Aim
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information,	Not applicable (this is a protocol)

		including the registration number.	
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	Page 3-5, Inclusion criteria
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	Page 5, Searching and screening
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Appendix 2
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	Page 6, Management of searching and screening
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	Page 6-8, Data coding
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	Page 6-8, Data coding
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	Page 8-9, Quality assessment of included studies

Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	Page 9-10, Evidence map; Synthesis
RESULTS			
-	14-18	-	Not applicable – this is a protocol
DISCUSSION			
-	19-21	-	Not applicable – this is a protocol
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	Page 11, Funding

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.
* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.
† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).
‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.
§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

http://annals.org/aim/fullarticle/2700389/prisma-extension-scoping-reviews-prisma-scr-checklist-explanation

APPENDIX 2: MEDLINE search strategy

1 exp Fatigue Syndrome, Chronic/
2 Asthenia/
3 Neurasthenia/
4 akureyri disease.ti,ab.
5 Akuteyri disease.ti,ab.
6 atypical poliomyelitis.ti,ab.
7 benign myalgic encephalomyelitis.ti,ab.
8 CFIDS.ti,ab.
9 chronic fatigue*.ti,ab.
10 (chronic adj5 mononucleos*).ti,ab.
11 epidemic neuromyasthenia.ti,ab.
12 fatigue syndrom*.ti,ab.
13 myalgic encephalomyelit*.ti,ab.
14 neurasthenic neuroses.ti,ab.
15 neurasthenic syndrome*.ti,ab.
16 neurataxia.ti,ab.
17 neuroasthenia.ti,ab.
18 (neuromuscular adj6 fatigue).ti,ab.
19 (perspective adj5 asthenia).ti,ab.
20 post infectious encephalomyelitis.ti,ab.
21 postviral fatigue syndrome*.ti,ab.
22 PVFS.ti,ab.
23 royal free disease*.ti,ab.
24 "Neuro Inflammatory and Oxidative fatigue".ti,ab.
25 NIOF.ti,ab.
26 Post exertion.ti,ab.
27 Post exertional.ti,ab.
28 PEM.ti,ab.
29 Systemic Exertion Intolerance Disease.ti,ab.
30 ME CFS.ti,ab.
31 or/1-30
32 exp animals/ not humans.sh.
33 31 not 32
34 limit 33 to english language
35 (2018* or 2019* or 2020* or 2021* or 2022* or 2023*).ed.
36 34 and 35

Footnote: Search strategy lines 2-7, 9-11 and 14-19 are terms commonly associated with outdated views of ME/CFS. These terms have been included in order to ensure that a comprehensive map of evidence in this field is produced. The protocol for this evidence map recognises the importance of using up-to-date, accepted, diagnostic criteria for ME/CFS, and the diagnostic criteria used in studies will be central to the evidence maps produced. The primary output will be an evidence map which is limited to studies in which post-exertional malaise was a key component of the diagnostic criteria adopted during the study (I.e. CCC, ICC or IOM criteria). The identification of studies of populations which authors describe as people with ME/CFS, but which use out-dated diagnostic criteria, could play an important role in highlighting gaps/limitations in the current evidence base. This comprehensive search strategy will ensure that we can identify these studies.

APPENDIX 3: PSP questions mapped to key themes and subcategories

Key theme	Sub-themes	PSP questions
Risk factor association	Biological mechanisms	P1a
	Immune system factors	P4a/b
	Infection (including Covid-19)	P6a
	Central and peripheral nervous system function	P7a
	Genetic factors	P8a, 8b
	Oxygen (delivery, use)	P10+a
	Mitochondria	P10a
	Different types with different causes and severity	P5a / P9 (some overlap in these questions)
	Environmental factors	-
	Social factors	-
	Demographic factors	-
Diagnostic assessment	Current assessments / tools for ME/CFS	P3
Treatment / management	Pharmacological	-
	Non-pharmacological	-
	Service provision and delivery	-
	Other	-
Natural history / prognosis	Recovery patterns of ME/CFS	-
	Different types of ME/CFS	P5c
Other		

PSP Questions:

- **P1 a Priority 1:** What is the biological mechanism that causes post-exertional malaise (symptoms caused or made worse by physical, mental or emotional effort, which can be delayed) in people with ME/CFS?
- **P1 b** How is this best treated and managed?

- **P2 Priority 2:** Which existing drugs used to treat other conditions might be useful for treating ME/CFS, such as low dose naltrexone, or drugs used to treat Postural Orthostatic Tachycardia Syndrome (POTS)?

- **P3 Priority 3:** How can an accurate and reliable diagnostic test be developed for ME/CFS?

- **P4a Priority 4:** Is ME/CFS caused by a faulty immune system?
- **P4b** Is ME/CFS an autoimmune condition?

- **P5a Priority 5:** Are there different types of ME/CFS linked to different causes and how severe it becomes?

- **P5b** Do different types of ME/CFS need different treatments or
- **P5c** have different chances of recovery?

- **P6a Priority 6:** Why do some people develop ME/CFS following an infection?
- **P6b** Is there a link with long-COVID?

- **P7a Priority 7:** What causes the central and peripheral nervous systems (brain, spinal cord and nerves in the body) to malfunction in people with ME/CFS?
- **P7b Could** this understanding lead to new treatments?

- **P8a Priority 8:** Is there a genetic link to ME/CFS?
- **P8b** If yes, how does this affect the risk of ME/CFS in families?
- **P8c** Could this lead to new treatments?

- **P9 Priority 9:** What causes ME/CFS to become severe?

- **P10a Priority 10:** How are mitochondria, responsible for the body's energy production, affected in ME/CFS?
- **P10b?** Could this understanding lead to new treatments?

- **P10+a Priority 10+:** Does poor delivery or use of oxygen within the body cause ME/CFS symptoms?
- **P10+b** If so, how is this best treated?

Notes:

PSP questions not covered by proposed evidence map: The PSP questions are broad and multifaceted. This proposed evidence map will demonstrate the volume of research addressing key topics but will not directly answer the PSP questions. Further systematic reviews would be required in order to do this. Further:

- PSP question 2 is about **pharmacological** treatments for *conditions other than ME/CFS* which may be beneficial to people living with ME/CFS. It would not be possible to cover this broad question in a mapping review, in which the searching would be limited to evidence directly related to ME/CFS.
- Treatments – several of the questions have a 'treatment' component, often linked to a question about risk factor. To comprehensively map intervention studies across these questions is beyond the scope of our proposed evidence map. For efficiency, while mapping the evidence in this field, we propose identifying and doing a 'top' level categorisation of the intervention studies. However, we do not propose detailed mapping of the intervention studies; this would require additional data extraction and another evidence map (and therefore additional time).

APPENDIX 4: CRediT author statement

Term	Definition	Contributors
Conceptualization	Ideas; formulation or evolution of overarching research goals and aims	ATB, JP, PC, SM, ME Research Collaborative Patient Advisory Group (MERC PAG), ME/CFS Research Working Group
Methodology	Development or design of methodology; creation of models	ATB, PC, BD, KT, CB, CS, JC
Software	Programming, software development; designing computer programs; implementation of the computer code and supporting algorithms; testing of existing code components; designing of search strategies	CF, PC
Validation	Verification, whether as a part of the activity or separate, of the overall replication/ reproducibility of results/experiments and other research outputs	n/a
Formal analysis	Application of statistical, mathematical, computational, or other formal techniques to analyse or synthesize study data	n/a
Investigation	Conducting a research and investigation process, specifically performing the experiments, or data/evidence collection	n/a
Resources	Provision of study materials, reagents, materials, patients, laboratory samples, animals, instrumentation, computing resources, or other analysis tools	n/a
Data Curation	Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later reuse	MS, ATB, CF, PC
Writing - Original Draft	Preparation, creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation)	ATB
Writing - Review & Editing	Preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre-or postpublication stages	JP, MS, PC, other members of the NESSIE team, MERC PAG, ME/CFS Research Working Group

Visualization	Preparation, creation and/or presentation of the published work, specifically visualization/ data presentation	n/a
Supervision	Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team	ATB, PC, MS, JP
Project administration	Management and coordination responsibility for the research activity planning and execution	ATB, PC, MS
Funding acquisition	Acquisition of the financial support for the project leading to this publication	n/a