National Institute for Health and Care Excellence

Final

Myalgic encephalomyelitis (or encephalopathy) / chronic fatigue syndrome: diagnosis and management

[E] Management strategies before diagnosis

NICE guideline NG201

Evidence reviews underpinning recommendations and research recommendations in the NICE guideline

August 2021

Final

These evidence reviews were developed by the National Guideline Centre

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1.1 Review question

1 What is the clinical and cost effectiveness of pre diagnosis management strategies for people with symptoms consistent with ME/CFS but are not clinically diagnosed?

1.1.1 Introduction

A diagnosis of ME/CFS is based on clinical history and the criteria for a diagnosis of ME/CFS include a minimum time period during which symptoms are present and persistent. Some people may present to healthcare professionals with symptoms consistent with ME/CFS but do not yet meet the criteria for diagnosis of ME/CFS. The need to consider alternate diagnoses and await investigation or specialist opinion may all contribute to delay in diagnosis. The committee were interested in management strategies during this period that might improve outcomes for people with suspected ME/CFS.

This review aims to determine the effectiveness of pre diagnosis management strategies for people experiencing symptoms suggestive of ME/CFS.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of pre-diagnosis management strategies review question

Population	Adults, children and young people who are experiencing symptoms consistent with ME/CFS, but are not clinically diagnosed.
Interventions	• Pharmacological interventions/management • Non-pharmacological interventions/management • Combinations of pharmacological and non pharmacological management
Comparisons	• No treatment • Each other (both within and between pharmacological and non pharmacological management strategies) • Placebo/control/usual care
Outcomes	CRITICAL OUTCOMES (at longest follow up available) • Quality of life (any validated scales) • Fatigue/fatiguability (any validated scales) • Patient satisfaction • Physical/cognitive functioning • Psychological status (may be separated into more specific outcomes, such as depression) • Pain (VAS) • Sleep quality (any validated scales) • Any treatment-related adverse effects IMPORTANT OUTCOMES (at longest follow up available) • Care needs • Impact on families and carers • Ability to resume occupation/school/study
Study design	• Systematic reviews • RCTs

- If no RCT evidence is available, search for non-randomised comparative studies will be considered. Non-randomised comparative studies will only include non-randomised trials and prospective/retrospective cohort studies.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A search was conducted for randomised controlled trials and non-randomised comparative studies comparing the effectiveness of pharmacological and non-pharmacological interventions versus each other, placebo or usual care/no treatment implemented as management strategies in people experiencing symptoms consistent with ME/CFS, but who are yet to be clinically diagnosed. No relevant randomised trials were identified. One relevant retrospective cohort study in young people was identified and included in the review[195] and is summarised in Table 2 below. Evidence from this study is summarised in the clinical evidence summary below (Table 3).See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E, and GRADE tables in Appendix F.

1.1.4.2 Excluded studies

See the excluded studies list in Appendix J.

1.1.4.3 Call for evidence

See the methods document for detail on the process and methods for the call for evidence.

The committee identified management strategies before diagnosis as an area of the scope with a lack of published evidence and proposed a call for evidence to identify any relevant literature not identified in the searches. Submissions were received from 42 separate organisations or individuals, consisting of 508 reports or references to publications (after removal of duplicates). All the 508 reports or references were checked for relevance to the review question according to the review protocol, all were excluded. For details why submitted evidence was not relevant see call for evidence excluded studies list in Appendix J.

1.1.5 Summary of the study included in the effectiveness evidence

Table 2: Summary of study included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Gill 2004[195]	Inpatient management (n=5): Admission to the hospital involved 1 to 4 weeks on the adolescent ward, daily physiotherapy to institute a graded exercise regime, attendance at the hospital school, and involvement of the adolescent counsellors of the psychiatry team. The subjects' agreement to return to their own school at discharge was a condition of entering the program. Versus Outpatient management (n=3): Subjects managed as outpatients were educated about the course and management of CFS and encouraged to return to school and engage in a graded exercise program.	N=8 people with symptoms consistent with CFS, yet to be clinically diagnosed. These participants had been referred to a specialist service with prominent fatigue and symptoms consistent with CFS but failed to meet the definition (1994 CDC criteria) as symptom duration was less than 6 months. Strata details: young people, severity mixed or unclear (adolescents, mean age 13.84 years (SD 2.07).	CRITICAL OUTCOMES: Quality of life (dichotomous outcomes – near or complete improvement in symptoms; no improvement or worsening and meet CFS definition) IMPORTANT OUTCOMES: Ability to resume occupation/school/study (dichotomous outcomes – number who attended school or work part-time for more than 2 years from diagnosis; number who have resumed normal activities)	Conducted in Australia. Retrospective cohort study. A questionnaire administered by telephone was used to collect outcome data. Participants were divided into 3 groups: 1) those with CFS, 2) those with idiopathic chronic fatigue (according to 1994 CDC criteria), and 3) those with prominent fatigue/symptoms consistent with CFS but failed to meet the definition as symptom duration was less than 6 months. Only data from the third group is relevant to this protocol. No participants in this group were eventually diagnosed with CFS. Very serious population indirectness: unclear if participants would have gone on to develop ME/CFS without intervention and study used 1994 CDC criteria which does not include PEM as a compulsory feature. Other outcomes were reported but results were not separated by intervention: Dichotomous: number with current fatigue, number with fatigue when enjoying an activity, number exercising regularly, number receiving counselling;

Study	Intervention and comparison	Population	Outcomes	Comments
				Continuous: estimate of current best level of activity (1-10 scale), days tired per week, symptoms over the last month, time from diagnosis to return to school, days of school missed in the past year.

See Appendix D for full evidence tables.

1.1.6 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: inpatient versus outpatient management

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with inpatient versus outpatient management (95% CI)
Quality of life: near or complete improvement	8 (1 study) 5.84 years	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 1 (0.64 to 1.56)	Moderate	
				1000 per 1000	0 fewer per 1000 (from 360 fewer to 560 more)
Quality of life: no improvement or worsening and meet CFS definition	8 (1 study) 5.84 years	⨁⊖⊖⊖ VERY LOW1,2,4 due to risk of bias, indirectness, imprecision	RD 0 (-0.39 to 0.39)	Moderate	
				0 per 1000	0 fewer per 1000 (from 390 fewer to 390 more)
Ability to resume occupation/school/study: number who have resumed normal activities	8 (1 study) 5.84 years	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 1 (0.64 to 1.56)	Moderate	
				1000 per 1000	0 fewer per 1000 (from 360 fewer to 560 more)
Ability to resume occupation/school/study: number who attended school or work part time for more than 2 years from diagnosis	8 (1 study) 5.84 years	⨁⊖⊖⊖ VERY LOW1,2,4 due to risk of bias, indirectness, imprecision	RD 0 (-0.39 to 0.39)	Moderate	
				0 per 1000	0 fewer per 1000 (from 390 fewer to 390 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with inpatient versus outpatient management (95% CI)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the majority of the evidence included an indirect population or by 2 increments if the majority of the evidence included a very indirect population. Downgraded by 2: 1) unclear if participants would have gone on to develop ME/CFS without intervention; 2) study used 1994 CDC criteria which does not include PEM as a compulsory feature.
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs (MID = minimally important difference, see Methods Chapter of guideline for more information)
4 Zero events in both arms - downgraded by 1 increment if the sample size is between 70 and 350, and downgraded by 2 increments if the sample size is less than 70

See Appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

No health economic studies were included.

1.1.7.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G.

1.2 The committee's discussion and interpretation of the evidence

The committee discussed this evidence with the findings from the reviews on Information for people with ME/CFS and their families and carers (report A), Information and Support for health and social care professionals (report B), access to care (report C), Diagnosis (D) non pharmacological management (report G) and the report on Children and Young people (Appendix 1). Where relevant this is noted.

1.2.1 The outcomes that matter most

Quality of life, fatigue/fatigability, patient satisfaction, physical function, cognitive function, psychological status, pain, sleep quality, treatment-related adverse events were agreed by the committee to be critical outcomes for decision making.

The committee was aware of concerns from the ME/CFS community that delays in diagnosis and the potential for inappropriate advice on activity and rest could result in deterioration of symptoms and poorer prognosis for people who are later diagnosed with ME/CFS. Fatigue/fatigability, unrefreshing sleep and physical and cognitive dysfunction are recognised as key symptoms of ME/CFS. The worsening or improvement of these symptoms reflect the impact of an intervention or strategy. The committee agreed that pain though not key to the diagnosis of ME/CFS, is a common symptom in people with ME/CFS and should be considered by the committee in their decision making. The committee agreed that any decisions on interventions and strategies should be informed by treatment related adverse events as a possible indicator of harm.

Care needs, impact on families and carers and ability to resume occupation, school or study were considered important outcomes for decision making. Management interventions and strategies implemented before diagnosis are intended for short term support to prevent deterioration of symptoms. The committee was also interested in any potential benefit in the longer term. The diagnosis of ME/CFS can be delayed and any intervention that would impact longer term outcomes may be important.

The committee acknowledged the lack of existing objective outcome measures of effectiveness of interventions for ME/CFS and the limitations of subjective measures (see Professor Edwards expert testimony – Appendix 3: Expert testimonies). Only validated outcome measurement scales were included in the evidence review.

1.2.2 The quality of the evidence

Several RCTs were identified that included populations with fatigue, including some with additional symptoms consistent with ME/CFS. These populations included people diagnosed with post viral fatigue syndrome, idiopathic chronic fatigue and CFS-like illness. The studies did not report whether these people were subsequently diagnosed with ME/CFS. It was therefore not possible to know whether the symptoms were related to ME/CFS or some other cause or whether any of the participants would have gone on to develop ME/CFS without the interventions. These studies were therefore excluded from the review.

One non-randomised study was included in the review as the participants at the time of intervention (people referred with a possible diagnosis of CFS, described as having symptoms consistent with CFS but failing to meet the definition, as symptom duration was less than 6 months) met the population criteria in the review protocol and diagnosis at follow up was reported. However, the committee noted several important limitations of the evidence.

Evidence was only identified for quality of life and ability to resume school in young people with a mean age of 13.84 years. All the evidence was very low quality. The evidence was

downgraded for study design, and very serious risk of bias, indirectness and imprecision. The committee noted all the evidence came from 1 small non-randomised study with 8 participants, with allocation to groups based on consecutive patients in a clinic. The study only included subjective outcomes with data collection by telephone questionnaire up to 5 years after the intervention. No evidence was identified for children or adults.

In particular, the committee noted that although the participants at the time of intervention met the population criteria in the review protocol (adults, children and young people who are experiencing symptoms consistent with ME/CFS, but who are yet to be clinically diagnosed) at follow up none of them met the CDC 1994 criteria for a diagnosis of ME/CFS. This is problematic as it is not clear if the participants ever had ME/CFS and if their symptoms at the time of the study enrolment were a result of another condition. If this is the case the participants are not the population set out in the review protocol. Another explanation could be that the participants in both groups did not develop ME/CFS as a result of the interventions.

The committee agreed it was not possible to make any conclusions based on the evidence. In one interpretation the study has an indirect population (they do not have ME/CFS) and in the other the assumption that these interventions result in young people not developing ME/CFS is potentially a harmful generalisation of the very low quality evidence.

After reviewing the evidence, the committee agreed it was not useful in supporting their decision making on pre diagnosis interventions and strategies.

1.2.3 Benefits and harms

The committee acknowledged there is a lack of evidence on management strategies and interventions before a diagnosis of ME/CFS. The committee considered that the time period between suspicion of ME/CFS and diagnosis can be an anxious time for people with these symptoms and agreed to make consensus recommendations based on their own experience and taking into account the evidence from findings from the reviews on Information for people with ME/CFS and their families and carers (report A), Information and Support for health and social care professionals (report B), access to care (report C), Diagnosis (D) non pharmacological management (report G) and the report on Children and Young people (Appendix 1).

The committee noted that people with ME/CFS report delays in diagnosis. The reasons for delays in diagnosis are explored further in the evidence reports (see Evidence review A: Information for health and social care professionals, Evidence review C: Access to care, and Evidence review D: Diagnosis). The committee agreed that in their experience delays in diagnosis can have a negative impact on a person's physical and emotional health, with the potential worsening of symptoms and deterioration in health. People waiting for a diagnosis have reported receiving little or no support and inappropriate information on managing the symptoms they are experiencing (see Evidence review C: Access to care). This reinforced the committee's opinion that it was important to make consensus recommendations for people when ME/CFS is suspected to ensure they receive advice without having to wait for a diagnosis to be confirmed by a ME/CFS specialist service. This was also seen as important to the person, validating the symptoms they are experiencing and that they are believed.

The key features of ME/CFS are debilitating fatigue, post exertional malaise, unrefreshing sleep and cognitive difficulties (see Evidence review D: Diagnosis). When these symptoms are present for a minimum of 6 weeks in adults and 4 weeks in children and young people ME/CFS is suspected. The committee agreed it was important to give prompt advice on how to manage and reduce the impact of symptoms. The committee stated this advice should be given while waiting for a diagnosis to potentially avoid worsening symptoms.

The committee noted there is NICE guidance on how to manage some of the symptoms that are commonly reported by people with ME/CFS and this guidance is referenced in the

recommendations (for example, Neuropathic pain in adults). In addition, the committee have made recommendations on other symptoms commonly experienced by people with ME/CFS (see Evidence G: Non pharmacological management).

Based on their experience and the evidence the committee advised people with suspected ME/CFS to manage their energy levels by resting as needed, not pushing themselves by managing their daily activity and not pushing through their symptoms and maintaining a healthy balanced diet with adequate fluid intake.

The committee recognised this was different to the advice some people with suspected ME/CFS have been given about managing fatigue. For example, people have been told to push through pre-illness levels of activity or to exercise more despite experiencing debilitating fatigue as a result.

The committee did not make a recommendation on daytime sleep or naps due to a lack of evidence and a lack of agreement in the committee on a strategy that was suitable for all people with suspected ME/CFS. The committee are aware that in the early stages or acute phase of the illness some people find daytime sleep or naps beneficial, allowing for more meaningful activities to be achieved during the day; while other people have found daytime sleep or naps to be unrefreshing, potentially affecting the quality of sleep at night and contributing to sleep-wake reversal which can be difficult to regulate in the future.

The committee acknowledged there is a lack of evidence to support that advice to rest prevents deterioration and improves prognosis in people with suspected ME/CFS, but they agreed the advice would not be harmful in the short term. This was also an important consideration when the committee recognised that some people with suspected ME/CFS may have a different condition or co-existing conditions and it was crucial that this recommendation would not result in harm to anyone.

The committee noted that throughout the evidence in the guideline (Evidence review C: Access to care) people with ME/CFS describe long waits for diagnosis and uncertainty about the pathway for diagnosis. The committee agreed it was important that people with suspected ME/CFS are kept informed about the process for diagnosis and the time they can expect to wait. The committee made a consensus recommendation to advise people with suspected ME/CFS that their diagnosis can only be confirmed after 3 months of persistent symptoms.

The committee discussed the importance of people with suspected ME/CFS being aware of changes in their symptoms. The committee noted there is a lack of awareness that ME/CFS is a fluctuating condition in which a person's symptoms can change unpredictably in nature and severity over days, weeks and made recommendations to raise awareness about this in the principles of care for people with ME/CFS and Information and support sections of the guideline. This is important for people with suspected ME/CFS to be aware of and to know that if they develop new or worsening symptoms they can return to their GP for advice. The committee made a consensus recommendation to reinforce this in the guideline section on advice for people with suspected ME/CFS.

This discussion has focused on advice being given to people with a short duration of symptoms. The committee were aware that clinicians do encounter people who have not been diagnosed with ME/CFS but have had symptoms consistent with ME/CFS and been unwell for many months and in some cases years. These people would benefit from the same advice but should be diagnosed and referred to specialist services without delay.

Children and young people with suspected ME/CFS

The committee noted the identified evidence was conducted on young people but as detailed above they were not confident using the evidence to make any recommendations. The committee used their own experience and evidence from the Children and young people report (Appendix 1) to inform their decision making for children and young people.

The journey to diagnosis for children and young people was identified as one of the key themes in the report findings. The participants describe their symptoms initially as a resolvable short-term illness but it soon became apparent they were experiencing something that was unknown and different. The symptoms lasted longer, were more debilitating and felt like a more serious illness. The understanding of their experiences, the process and how to manage their illness was difficult initially for all the participants. This was compounded by a lack of knowledge the healthcare professionals they met had about ME/CFS. Some of the participants expressed anger at the lack of support and advice they received before a diagnosis relying on research they or family members had done. The participants identified the need for an earlier diagnosis to reduce the extreme experience of symptoms.

This resonated with the committee's experiences, and they agreed that the recommendations on management strategies before diagnosis equally applied to children and young people.

In addition, the committee noted the participants highlighted increased periods of time away from school and the negative impact this had on their education and not being able to see friends. The committee reflected that when children and young people have symptoms that are consistent with ME/CFS the impact on their education or training can be immediate and can result in them being disadvantaged and missing out on education. To address this the committee agreed it was important that the child or young person's place of education or training was contacted as soon as possible once ME/CFS is suspected. This contact was important to provide education about ME/CFS (for example, the impact of schools being high stimulus environments) and to advise about any flexible adjustments or adaptions. In the committee's experience this helps to minimise the disruption to the child or young person's education or training. Some of the committee members recalled experiences where classmates as well as the teacher had received information about ME/CFS and this had had a positive impact in increasing the understanding and support the child or young person received. The adjustments and adaptions are discussed by the committee in the report on information and support for people with ME/CFS (Evidence report A).

Taking this into account the committee recommended that when ME/CFS is suspected in a child or young person the GP should work with the child or young person's place of education or training to advise about flexible adjustments or adaptations.

1.2.4 Cost effectiveness and resource use

There were no published economic evaluations for managing people suspected of having unconfirmed ME/CFS.

Since there was not good quality evidence of clinical effectiveness, the cost effectiveness of specific interventions remains unproven.

Given the lack of evidence the committee decided to primarily recommend the management of symptoms, using treatments that have been shown to be cost effective in other NICE guidelines.

Based on their experience, the committee also recommended advising these people to stay within their energy limits and maintain healthy eating and sleeping habits. This advice would not impose a significant cost on the NHS and if it leads to fewer patients deteriorating then it would be highly cost effective.

Appendices

Appendix A Review protocols

ID	Field	Content
0.	PROSPERO registration number	1. Not registered
1.	Review title	What is the clinical and cost effectiveness of pre diagnosis management strategies for people experiencing symptoms consistent with ME/CFS but are not clinically diagnosed?
2.	Review question	What is the clinical and cost effectiveness of pre diagnosis management strategies for people experiencing symptoms consistent with ME/CFS?
3.	Objective	As there is no diagnostic test for ME/CFS, diagnosis is based on assessment of signs and symptoms and clinical history. Several different definitions and diagnostic criteria are used in clinical practice, and symptoms can take time to develop, meaning some people do not meet the criteria for diagnosis of ME/CFS immediately. However, these people still need support in managing their symptoms. In addition, exclusion of differential diagnoses may delay formal diagnosis as well, even in the absence of a mandatory diagnostic delay period. Therefore, this review aims to determine the clinical and cost effectiveness of pre-diagnosis management strategies for people experiencing symptoms consistent with ME/CFS.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR)

		• Embase • MEDLINE • Cinahl Searches will be restricted by: • English language • Human studies • Letters and comments are excluded. Other searches: • Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review
5.	Condition or domain being studied	ME/CFS
6.	Population	Adults, children and young people who are experiencing symptoms suggestive of ME/CFS, but who are yet to be clinically diagnosed.

7.	Intervention/Exposure/Test	• Pharmacological management
		• Non-pharmacological management, for example:
		  ○ Self-management strategies (Diaries)
		  ○ Occupational/school advice
		  ○ Psychological interventions/support

		○ Exercise interventions ○ Activity management (includes rest/convalescence) ○ Lifestyle advice ○ Dietary advice ○ Sleep interventions ○ Complementary therapies • Combinations of pharmacological and non- pharmacological management
8.	Comparator/Reference standard/Confounding factors	• No treatment • Each other (both within and between pharmacological and non pharmacological management strategies) • Placebo/control/usual care
9.	Types of study to be included	• Systematic reviews • RCTs If no RCT evidence is available, search for non-randomised comparative studies will be considered. Non-randomised comparative studies will only include non-randomised trials and prospective/retrospective cohort studies.
10.	Other exclusion criteria	Non-English language studies.

11.	Context	N/A
12.	Primary outcomes (critical outcomes)	CRITICAL OUTCOMES (at longest follow up available) • Quality of life (any validated scales) • Fatigue/fatiguability (any validated scales) • Patient satisfaction • Physical/cognitive functioning • Psychological status (may be separated into more specific outcomes, such as depression or anxiety) • Pain (VAS) • Sleep quality (any validated scales) • Any treatment-related adverse effects
13.	Secondary outcomes (important outcomes)	IMPORTANT OUTCOMES (at longest follow up available) • Care needs • Impact on families and carers • Ability to resume occupation/school/study
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above.

		10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. A second reviewer will quality-assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For intervention reviews the following checklist will be used according to study design being assessed: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) Non randomised study:including cohort studies:Cohrane ROBINS-I Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.

16.	Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. If the population included in an individual study includes children aged under 12, it will be included if the majority of the population is aged over 12, and downgraded for indirectness if the overlap into those aged less than 12 is greater than 20%. Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent. Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.

17.	Analysis of sub-groups	• <u>Stratification:</u> • Age: children vs young people vs adults • Severity of presenting symptoms: severe vs not severe <u>Subgroups to investigate if heterogeneity is present</u> • Diagnostic criteria used in study (each set of criteria is a separate sub-group) • Type of onset (gradual/sudden [in less than 1 week]) • Earlier [within 1 month of presentation] vs later [>1 month after presentation] pre-diagnosis management (outcomes for later management may be worse) • Studies where analysis restricted to randomised participants who were later diagnosed with ME/CFS vs studies where all (regardless of final diagnosis) are kept together
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)

19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	01/01/20		
22.	Anticipated completion date	01/01/21		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☑	☐
		Piloting of the study selection process	☑	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐

		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** National Guideline Centre **5b Named contact e-mail** **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with		

		section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10091
28.	Other registration details	
29.	Reference/URL for published protocol	
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
31.	Keywords	
32.	Details of existing review of same topic by same authors	N/A
33.	Additional information	N/A
34.	Details of final publication	www.nice.org.uk

Table 4: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2004, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[367] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and

	methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2004 or later but that depend on unit costs and resource data entirely or predominantly from before 2004 will be rated as 'Not applicable'. • Studies published before 2004 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B Literature search strategies

This literature search strategy was used for the following review question:

- What is the clinical and cost effectiveness of pre diagnosis management strategies for people with symptoms consistent with ME/CFS?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[367]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve.

Searches for patient views were run in Medline (OVID), Embase (OVID), CINAHL, and PsycINFO (ProQuest).

Table 5: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 23 June 2020	Exclusions
Embase (OVID)	1974 – 23 June 2020	Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 6 of 12 CENTRAL to 2020 Issue 6 of 12	None
CINAHL, Current Nursing and Allied Health Literature (EBSCO)	Inception – 23 June 2020	None
PsycINFO (ProQuest)	Inception – 23 June 2020	Exclusions
Epistemonikos (The Epistemonikos Foundation)	Inception - 23 June 2020	None

Medline (Ovid) search terms

1.	Fatigue Syndrome, Chronic/
2.	chronic* fatigue*.ti,ab.
3.	(fatigue* adj2 (disorder* or syndrome* or post viral or postviral or immune dysfunction* or post infection* or postinfection*)).ti,ab.
4.	((myalgic or post infection* or postinfection*) adj (encephalomyelitis or encephalopathy)).ti,ab.
5.	((ME adj CFS) or (CFS adj ME) or CFIDS or PVFS).ti,ab.
6.	(Systemic Exertion Intolerance Disease or SEID).ti,ab.
7.	((CFS adj SEID) or (SEID adj CFS) or (ME adj CFS adj SEID) or (ME adj SEID) or (SEID adj ME)).ti,ab.
8.	((Orthostatic intolerance or postural orthostatic tachycardia syndrome or postural tachycardia syndrome or POTS) adj6 (CFS or chronic* fatigue* or ME or myalgic or SEID or systemic exertion)).ti,ab.

9.	((Post-exertional or postexertional) adj2 malaise).ti,ab.
10.	(neurasthenic neuroses or epidemic neuromyasthenia or neurataxia or neuroasthenia or neurasthenia).ti,ab.
11.	((atypical or simulating or resembling) adj poliomyelitis).ti,ab.
12.	((chronic adj2 epstein Barr virus) or CEBV or CAEBV or chronic mononucleosis).ti,ab.
13.	xenotropic murine leukemia virus-related virus.ti,ab.
14.	effort syndrome*.ti,ab.
15.	(((akureyri or iceland or tapanui or royal free or royal free hospital) adj disease*) or ((yuppie or yuppy or tapanui) adj flu)).ti,ab.
16.	or/1-15
17.	letter/
18.	editorial/
19.	news/
20.	exp historical article/
21.	Anecdotes as Topic/
22.	comment/
23.	case report/
24.	(letter or comment*).ti.
25.	or/17-24
26.	randomized controlled trial/ or random*.ti,ab.
27.	25 not 26
28.	animals/ not humans/
29.	exp Animals, Laboratory/
30.	exp Animal Experimentation/
31.	exp Models, Animal/
32.	exp Rodentia/
33.	(rat or rats or mouse or mice).ti.
34.	or/27-33
35.	16 not 34
36.	limit 35 to English language

Embase (Ovid) search terms

1.	chronic fatigue syndrome/
2.	chronic* fatigue*.ti,ab.
3.	(fatigue* adj2 (disorder* or syndrome* or post viral or postviral or immune dysfunction* or post infection* or postinfection*)).ti,ab.
4.	((myalgic or post infection* or postinfection*) adj (encephalomyelitis or encephalopathy)).ti,ab.
5.	((ME adj CFS) or (CFS adj ME) or CFIDS or PVFS).ti,ab.
6.	(Systemic Exertion Intolerance Disease or SEID).ti,ab.
7.	((CFS adj SEID) or (SEID adj CFS) or (ME adj CFS adj SEID) or (ME adj SEID) or (SEID adj ME)).ti,ab.
8.	((Orthostatic intolerance or postural orthostatic tachycardia syndrome or postural tachycardia syndrome or POTS) adj6 (CFS or chronic* fatigue* or ME or myalgic or SEID or systemic exertion)).ti,ab.
9.	((Post-exertional or postexertional) adj2 malaise).ti,ab.

10.	(neurasthenic neuroses or epidemic neuromyasthenia or neurataxia or neuroasthenia or neurasthenia).ti,ab.
11.	((atypical or simulating or resembling) adj poliomyelitis).ti,ab.
12.	((chronic adj2 epstein Barr virus) or CEBV or CAEBV or chronic mononucleosis).ti,ab.
13.	xenotropic murine leukemia virus-related virus.ti,ab.
14.	effort syndrome*.ti,ab.
15.	(((akureyri or iceland or tapanui or royal free or royal free hospital) adj disease*) or ((yuppie or yuppy or tapanui) adj flu)).ti,ab.
16.	or/1-15
17.	letter.pt. or letter/
18.	note.pt.
19.	editorial.pt.
20.	case report/ or case study/
21.	(letter or comment*).ti.
22.	or/17-21
23.	randomized controlled trial/ or random*.ti,ab.
24.	22 not 23
25.	animal/ not human/
26.	nonhuman/
27.	exp Animal Experiment/
28.	exp Experimental Animal/
29.	animal model/
30.	exp Rodent/
31.	(rat or rats or mouse or mice).ti.
32.	or/24-31
33.	16 not 32
34.	limit 33 to English language

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Fatigue Syndrome, Chronic] this term only
#2.	chronic* fatigue*:ti,ab
#3.	(fatigue* near/2 (disorder* or syndrome* or post viral or postviral or immune dysfunction* or post infection* or postinfection*)):ti,ab
#4.	((myalgic or post infection* or postinfection*) near/1 (encephalomyelitis or encephalopathy)):ti,ab
#5.	((ME near/1 CFS) or (CFS near/1 ME) or CFIDS or PVFS):ti,ab
#6.	(Systemic Exertion Intolerance Disease or SEID):ti,ab
#7.	((CFS near/1 SEID) or (SEID near/1 CFS) or (ME near/1 CFS near/1 SEID) or (ME near/1 SEID) or (SEID near/1 ME)):ti,ab
#8.	(Orthostatic intolerance or postural orthostatic tachycardia syndrome or postural tachycardia syndrome or POTS)
#9.	((Post-exertional or postexertional) near/2 malaise):ti,ab
#10.	(neurasthenic neuroses or epidemic neuromyasthenia or neurataxia or neuroasthenia or neurasthenia):ti,ab
#11.	((atypical or simulating or resembling) near/1 poliomyelitis):ti,ab
#12.	((chronic epstein Barr virus) or CEBV or CAEBV or chronic mononucleosis):ti,ab
#13.	xenotropic murine leukemia virus-related virus:ti,ab
#14.	effort syndrome*:ti,ab

#15.	((akureyri or iceland or tapanui or "royal free" or "royal free hospital") near/1 disease*):ti,ab
#16.	((yuppie or yuppy or tapanui) near flu):ti,ab
#17.	(or #1-#16)

CINAHL (EBSCO) search terms

S1.	(MH "Fatigue Syndrome, Chronic")
S2.	chronic* fatigue*
S3.	(fatigue* n2 (disorder* or syndrome* or post viral or postviral or immune dysfunction* or post infection* or postinfection*))
S4.	((myalgic or post infection* or postinfection*) and (encephalomyelitis or encephalopathy))
S5.	((ME and CFS) or (CFS and ME) or CFIDS or PVFS)
S6.	(Systemic Exertion Intolerance Disease or SEID)
S7.	((CFS and SEID) or (SEID and CFS) or (ME and CFS and SEID) or (CFS and ME and SEID) or (ME and SEID) or (SEID and ME))
S8.	((Orthostatic intolerance or postural orthostatic tachycardia syndrome or postural tachycardia syndrome) and (CFS or chronic* fatigue* or ME or myalgic or SEID or systemic exertion))
S9.	((Post-exertional or postexertional) n2 malaise)
S10.	(neurasthenic neuroses or epidemic neuromyasthenia or neurataxia or neuroasthenia)
S11.	((atypical or simulating or resembling) and poliomyelitis)
S12.	(chronic epstein Barr virus or chronic mononucleosis)
S13.	xenotropic murine leukemia virus-related virus
S14.	effort syndrome*
S15.	(((akureyri or iceland or tapanui or royal free or royal free hospital) and disease*) or ((yuppie or yuppy or tapanui) and flu))
S16.	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15

PsycINFO (ProQuest) search terms

1.	((((chronic* fatigue*) OR (fatigue* NEAR2 (disorder* OR syndrome* OR post viral OR postviral OR immune dysfunction* OR post infection* OR postinfection*)) OR ((myalgic OR post infection* OR postinfection*) NEAR1 (encephalomyelitis OR encephalopathy)) OR ((ME NEAR1 CFS) OR (CFS NEAR1 ME) OR CFIDS OR PVFS) OR (Systemic Exertion Intolerance Disease OR SEID) OR ((CFS NEAR1 SEID) OR (SEID NEAR1 CFS)) OR ((ME NEAR1 CFS NEAR1 SEID) OR (ME NEAR1 SEID) OR (SEID NEAR1 ME)) OR ((Orthostatic intolerance OR postural orthostatic tachycardia syndrome OR postural tachycardia syndrome OR POTS) NEAR6 (CFS OR chronic* fatigue* OR ME OR myalgic OR SEID OR systemic exertion)) OR (neurasthenic neuroses OR epidemic neuromyasthenia OR neurataxia OR neuroasthenia OR neurasthenia) OR ((atypical OR simulating OR resembling) NEAR1 poliomyelitis)) OR (((chronic NEAR2 epstein Barr virus) OR CEBV OR CAEBV OR chronic mononucleosis) OR (xenotropic murine leukemia virus-related virus) OR (effort syndrome*) OR ((akureyri OR iceland OR tapanui OR royal free OR royal free hospital) NEAR1 disease*) OR ((yuppie OR yuppy OR tapanui) NEAR1 flu) OR MAINSUBJECT.EXACT.EXPLODE("Chronic Fatigue Syndrome"))) AND (stype.exact("Scholarly Journals") AND la.exact("ENG") AND po.exact("Human") NOT (me.exact("Empirical Study" OR "Quantitative Study" OR "Longitudinal Study" OR "Clinical Trial" OR "Qualitative Study" OR "Prospective Study" OR "Followup Study" OR "Literature Review" OR "Retrospective Study" OR "Systematic Review" OR "Meta Analysis") AND po.exact("Human"))

Epistemonikos search terms

1.	(advanced_title_en:((advanced_title_en:((chronic* fatigue* syndrome*) OR (fatigue* syndrome* OR fatigue* disorder* OR postviral fatigue* OR post viral fatigue* OR

	fatigue* immune dysfunction OR post infection fatigue* OR postinfection fatigue*) OR (encephalomyelitis OR encephalopathy) OR ("ME/CFS" OR "CFS/ME" OR "CFIDS" OR "PVFS") OR (Systemic Exertion Intolerance Disease OR SEID) OR ((CFS AND SEID) OR (SEID AND CFS) OR (ME AND CFS AND SEID) OR (ME AND SEID) OR (SEID AND ME)) OR (Orthostatic intolerance OR postural orthostatic tachycardia syndrome OR postural tachycardia syndrome OR POTS) OR ((Post-exertional OR postexertional) AND malaise) OR (neurasthenic neuroses OR epidemic neuromyasthenia OR neurataxia OR neuroasthenia OR neurasthenia) OR (atypical poliomyelitis OR simulating poliomyelitis OR resembling poliomyelitis) OR (chronic epstein Barr virus OR CEBV OR CAEBV OR chronic mononucleosis) OR (xenotropic murine leukemia virus-related virus) OR (effort syndrome*) OR (akureyri OR iceland disease OR tapanui OR royal free disease) OR (yuppie flu OR yuppy flu OR tapanui flu)) OR advanced_abstract_en:((chronic* fatigue* syndrome*) OR (fatigue* syndrome* OR fatigue* disorder* OR postviral fatigue* OR post viral fatigue* OR fatigue* immune dysfunction OR post infection fatigue* OR postinfection fatigue*) OR (encephalomyelitis OR encephalopathy) OR ("ME/CFS" OR "CFS/ME" OR "CFIDS" OR "PVFS") OR (Systemic Exertion Intolerance Disease OR SEID) OR ((CFS AND SEID) OR (SEID AND CFS) OR (ME AND CFS AND SEID) OR (ME AND SEID) OR (SEID AND ME)) OR (Orthostatic intolerance OR postural orthostatic tachycardia syndrome OR postural tachycardia syndrome OR POTS) OR ((Post-exertional OR postexertional) AND malaise) OR (neurasthenic neuroses OR epidemic neuromyasthenia OR neurataxia OR neuroasthenia OR neurasthenia) OR (atypical poliomyelitis OR simulating poliomyelitis OR resembling poliomyelitis) OR (chronic epstein Barr virus OR CEBV OR CAEBV OR chronic mononucleosis) OR (xenotropic murine leukemia virus-related virus) OR (effort syndrome*) OR (akureyri OR iceland disease OR tapanui OR royal free disease) OR (yuppie flu OR yuppy flu OR tapanui flu)))) OR advanced_abstract_en:((advanced_title_en:((chronic* fatigue* syndrome*) OR (fatigue* syndrome* OR fatigue* disorder* OR postviral fatigue* OR post viral fatigue* OR fatigue* immune dysfunction OR post infection fatigue* OR postinfection fatigue*) OR (encephalomyelitis OR encephalopathy) OR ("ME/CFS" OR "CFS/ME" OR "CFIDS" OR "PVFS") OR (Systemic Exertion Intolerance Disease OR SEID) OR ((CFS AND SEID) OR (SEID AND CFS) OR (ME AND CFS AND SEID) OR (ME AND SEID) OR (SEID AND ME)) OR (Orthostatic intolerance OR postural orthostatic tachycardia syndrome OR postural tachycardia syndrome OR POTS) OR ((Post-exertional OR postexertional) AND malaise) OR (neurasthenic neuroses OR epidemic neuromyasthenia OR neurataxia OR neuroasthenia OR neurasthenia) OR (atypical poliomyelitis OR simulating poliomyelitis OR resembling poliomyelitis) OR (chronic epstein Barr virus OR CEBV OR CAEBV OR chronic mononucleosis) OR (xenotropic murine leukemia virus-related virus) OR (effort syndrome*) OR (akureyri OR iceland disease OR tapanui OR royal free disease) OR (yuppie flu OR yuppy flu OR tapanui flu)) OR advanced_abstract_en:((chronic* fatigue* syndrome*) OR (fatigue* syndrome* OR fatigue* disorder* OR postviral fatigue* OR post viral fatigue* OR fatigue* immune dysfunction OR post infection fatigue* OR postinfection fatigue*) OR (encephalomyelitis OR encephalopathy) OR ("ME/CFS" OR "CFS/ME" OR "CFIDS" OR "PVFS") OR (Systemic Exertion Intolerance Disease OR SEID) OR ((CFS AND SEID) OR (SEID AND CFS) OR (ME AND CFS AND SEID) OR (ME AND SEID) OR (SEID AND ME)) OR (Orthostatic intolerance OR postural orthostatic tachycardia syndrome OR postural tachycardia syndrome OR POTS) OR ((Post-exertional OR postexertional) AND malaise) OR (neurasthenic neuroses OR epidemic neuromyasthenia OR neurataxia OR neuroasthenia OR neurasthenia) OR (atypical poliomyelitis OR simulating poliomyelitis OR resembling poliomyelitis) OR (chronic epstein Barr virus OR CEBV OR CAEBV OR chronic mononucleosis) OR (xenotropic murine leukemia virus-related virus) OR (effort syndrome*) OR (akureyri OR iceland disease OR tapanui OR royal free disease) OR (yuppie flu OR yuppy flu OR tapanui flu)))))

B.2 Health economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to ME/CFS population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated

after March 2015) and the Health Technology Assessment database (HTA – this ceased to be updated after March 2018), with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics.

Table 6: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 30 June 2020	Exclusions Health economics studies
Embase	2014 –30 June 2020	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - 2003 – 31 March 2018 NHSEED - 2003 to 31 March 2015	None

Medline (Ovid) search terms

1.	Fatigue Syndrome, Chronic/
2.	chronic* fatigue*.ti,ab.
3.	(fatigue* adj2 (disorder* or syndrome* or post viral or postviral or immune dysfunction* or post infection* or postinfection*)).ti,ab.
4.	((myalgic or post infection* or postinfection*) adj (encephalomyelitis or encephalopathy)).ti,ab.
5.	((ME adj CFS) or (CFS adj ME) or CFIDS or PVFS).ti,ab.
6.	(Systemic Exertion Intolerance Disease or SEID).ti,ab.
7.	((CFS adj SEID) or (SEID adj CFS) or (ME adj CFS adj SEID) or (ME adj SEID) or (SEID adj ME)).ti,ab.
8.	((Orthostatic intolerance or postural orthostatic tachycardia syndrome or postural tachycardia syndrome or POTS) adj6 (CFS or chronic* fatigue* or ME or myalgic or SEID or systemic exertion)).ti,ab.
9.	((Post-exertional or postexertional) adj2 malaise).ti,ab.
10.	(neurasthenic neuroses or epidemic neuromyasthenia or neurataxia or neuroasthenia or neurasthenia).ti,ab.
11.	((atypical or simulating or resembling) adj poliomyelitis).ti,ab.
12.	((chronic adj2 epstein Barr virus) or CEBV or CAEBV or chronic mononucleosis).ti,ab.
13.	xenotropic murine leukemia virus-related virus.ti,ab.
14.	effort syndrome*.ti,ab.
15.	(((akureyri or iceland or tapanui or royal free or royal free hospital) adj disease*) or ((yuppie or yuppy or tapanui) adj flu)).ti,ab.
16.	or/1-15
17.	letter/
18.	editorial/
19.	news/
20.	exp historical article/
21.	Anecdotes as Topic/
22.	comment/
23.	case report/
24.	(letter or comment*).ti.
25.	or/17-24

26.	randomized controlled trial/ or random*.ti,ab.
27.	25 not 26
28.	animals/ not humans/
29.	exp Animals, Laboratory/
30.	exp Animal Experimentation/
31.	exp Models, Animal/
32.	exp Rodentia/
33.	(rat or rats or mouse or mice).ti.
34.	or/27-33
35.	16 not 34
36.	limit 35 to English language
37.	Economics/
38.	Value of life/
39.	exp "Costs and Cost Analysis"/
40.	exp Economics, Hospital/
41.	exp Economics, Medical/
42.	Economics, Nursing/
43.	Economics, Pharmaceutical/
44.	exp "Fees and Charges"/
45.	exp Budgets/
46.	budget*.ti,ab.
47.	cost*.ti.
48.	(economic* or pharmaco?economic*).ti.
49.	(price* or pricing*).ti,ab.
50.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
51.	(financ* or fee or fees).ti,ab.
52.	(value adj2 (money or monetary)).ti,ab.
53.	or/37-52
54.	36 and 53

Embase (Ovid) search terms

1.	chronic fatigue syndrome/
2.	chronic* fatigue*.ti,ab.
3.	(fatigue* adj2 (disorder* or syndrome* or post viral or postviral or immune dysfunction* or post infection* or postinfection*)).ti,ab.
4.	((myalgic or post infection* or postinfection*) adj (encephalomyelitis or encephalopathy)).ti,ab.
5.	((ME adj CFS) or (CFS adj ME) or CFIDS or PVFS).ti,ab.
6.	(Systemic Exertion Intolerance Disease or SEID).ti,ab.
7.	((CFS adj SEID) or (SEID adj CFS) or (ME adj CFS adj SEID) or (ME adj SEID) or (SEID adj ME)).ti,ab.
8.	((Orthostatic intolerance or postural orthostatic tachycardia syndrome or postural tachycardia syndrome or POTS) adj6 (CFS or chronic* fatigue* or ME or myalgic or SEID or systemic exertion)).ti,ab.
9.	((Post-exertional or postexertional) adj2 malaise).ti,ab.

10.	(neurasthenic neuroses or epidemic neuromyasthenia or neurataxia or neuroasthenia or neurasthenia).ti,ab.
11.	((atypical or simulating or resembling) adj poliomyelitis).ti,ab.
12.	((chronic adj2 epstein Barr virus) or CEBV or CAEBV or chronic mononucleosis).ti,ab.
13.	xenotropic murine leukemia virus-related virus.ti,ab.
14.	effort syndrome*.ti,ab.
15.	(((akureyri or iceland or tapanui or royal free or royal free hospital) adj disease*) or ((yuppie or yuppy or tapanui) adj flu)).ti,ab.
16.	or/1-15
17.	letter.pt. or letter/
18.	note.pt.
19.	editorial.pt.
20.	case report/ or case study/
21.	(letter or comment*).ti.
22.	or/17-21
23.	randomized controlled trial/ or random*.ti,ab.
24.	22 not 23
25.	animal/ not human/
26.	nonhuman/
27.	exp Animal Experiment/
28.	exp Experimental Animal/
29.	animal model/
30.	exp Rodent/
31.	(rat or rats or mouse or mice).ti.
32.	or/24-31
33.	16 not 32
34.	limit 33 to English language
35.	health economics/
36.	exp economic evaluation/
37.	exp health care cost/
38.	exp fee/
39.	budget/
40.	funding/
41.	budget*.ti,ab.
42.	cost*.ti.
43.	(economic* or pharmaco?economic*).ti.
44.	(price* or pricing*).ti,ab.
45.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
46.	(financ* or fee or fees).ti,ab.
47.	(value adj2 (money or monetary)).ti,ab.
48.	or/35-47
49.	34 and 48

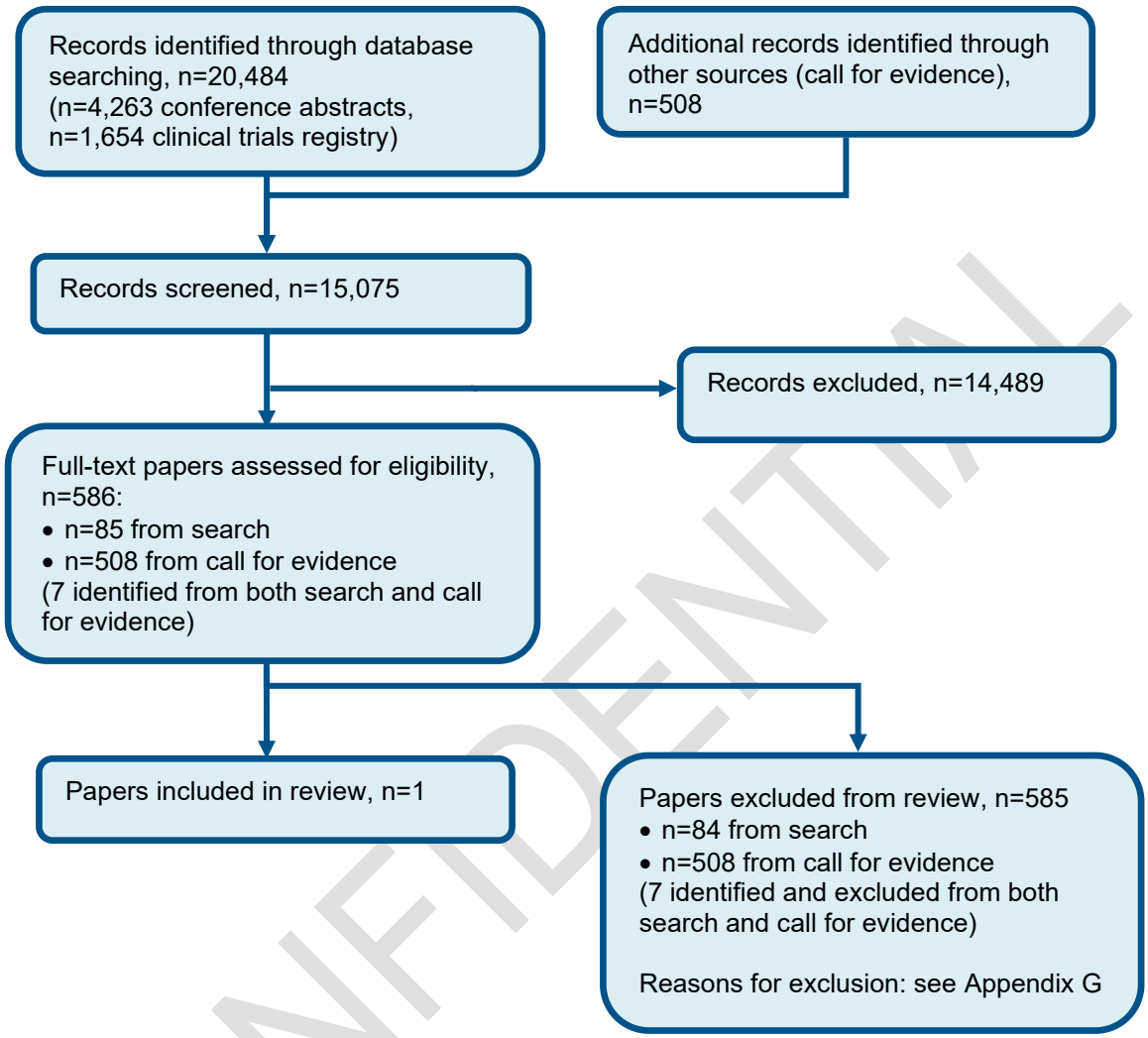
NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Fatigue Syndrome, Chronic

#2.	(chronic fatigue or fatigue syndrome*)
#3.	((myalgic adj (encephalomyelitis or encephalopathy)))
#4.	(((ME adj CFS) or (CFS adj ME)))
#5.	(post viral fatigue or post viral syndrome* or viral fatigue syndrome* or PVFS)
#6.	#1 OR #2 OR #3 OR #4 OR #5
#7.	(neurasthenic neuroses or epidemic neuromyasthenia or post infectious encephalomyelitis or neurataxia or neuroasthenia)
#8.	(((atypical or simulating or resembling) adj poliomyelitis))
#9.	(chronic epstein Barr virus or chronic mononucleosis)
#10.	(xenotropic murine leukemia virus-related virus)
#11.	(((chronic fatigue and immune dysfunction syndrome*) or cfids or chronic fatigue-fibromyalgia syndrome* or chronic fatigue disorder* or Systemic Exertion Intolerance Disease or SEID or effort syndrome or post infectious fatigue))
#12.	((((akureyri or iceland or tapanui or royal free or royal free hospital) adj disease*) or ((yuppie or yuppy or tapanui) adj flu)))
#13.	#7 OR #8 OR #9 OR #10 OR #11 OR #12
#14.	#6 or #13

Appendix C Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of pre-diagnosis management strategies



Appendix D Effectiveness evidence

D.1 Pre-diagnosis management strategies

Study	Gill 2004[195]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=10)
Countries and setting	Conducted in Australia; Setting: A tertiary referral hospital
Line of therapy	Unclear
Duration of study	Other: A questionnaire was designed and administered by telephone at a mean of 5.84 years after the initial examination.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Participants were divided into 3 groups: those with CFS, those with ICF (according to 1994 CDC criteria), and those with prominent fatigue/symptoms consistent with CFS but failed to meet the definition as symptom duration was less than 6 months. The third group is the population of interest for this review.
Stratum	young people - severity mixed or unclear : Adolescents
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Subjects referred with a possible diagnosis of CFS.
Exclusion criteria	Patients with other medical illnesses, including fatigue secondary to chronic pain states such as allodynia and fibromyalgia.
Recruitment/selection of patients	Consecutive patients referred with a possible diagnosis of CFS were identified.

Age, gender and ethnicity	Age - Mean (SD): 13.84 (2.07) years. Gender (M:F): 4/4. Ethnicity: NR
Further population details	Diagnostic criteria used: CDC 1994. ME/CFS status: Analysis including final diagnosis ME/CFS and non-ME/CFS (no patients in subgroup of interest went on to be diagnosed with ME/CFS) Type of onset : Not stated / Unclear
Extra comments	Number of minor criteria at baseline, mean (SD): 1.73 (1.56); symptom duration at baseline, mean (SD): 3.29 (1.52) months.
Indirectness of population	Very serious indirectness: 1) unclear if participants would have gone on to develop ME/CFS without intervention; 2) study used 1994 CDC criteria which does not include PEM as a compulsory feature.
Interventions	(n=5) Intervention 1: Non-pharmacological – inpatient management. Admission to the hospital involved 1 to 4 weeks on the adolescent ward, daily physiotherapy to institute a graded exercise regime, attendance at the hospital school, and involvement of the adolescent counsellors of the psychiatry team. The subjects' agreement to return to their own school at discharge was a condition of entering the program. Duration 1-4 weeks. Concurrent medication/care: Adolescents referred with symptoms suggestive of CFS attend the infectious diseases/immunology clinic for assessment, investigation, and treatment. If other medical illnesses are identified, patients are appropriately referred. The remainder are managed with a combination of education, exercise, counselling, and in some cases, admission to the hospital for 1 to 4 weeks. Once management has been instituted, most return to their local paediatrician or general practitioner for ongoing care. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. Timing of management: Not stated / Unclear (n=3) Intervention 2: Non-pharmacological – outpatient management. Subjects managed as outpatients were educated about the course and management of CFS and encouraged to return to school and engage in a graded exercise program. Duration Unclear. Concurrent medication/care: Adolescents referred with symptoms suggestive of CFS attend the infectious diseases/immunology clinic for assessment, investigation, and treatment. If other medical illnesses are identified, patients

	are appropriately referred. The remainder are managed with a combination of education, exercise, counselling, and in some cases, admission to the hospital for 1 to 4 weeks. Once management has been instituted, most return to their local paediatrician or general practitioner for ongoing care. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. Timing of management: Not stated / Unclear
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INPATIENT MANAGEMENT versus OUTPATIENT MANAGEMENT

Protocol outcome 1: Quality of life at longest follow ups
- Actual outcome for young people - severity mixed or unclear: Near or complete improvement at mean 5.84 years (SD 2.07); Group 1: 5/5, Group 2: 3/3; Comments: The responses to each survey question were compared across the subject groups. A qualitative assessment of each subject's responses by a single investigator enabled allocation to one of the following groups: complete or near complete recovery, improvement but with ongoing symptoms, or no improvement or worse and likely to still meet the CDC definition for CFS.
All patients reported to have made a complete or near complete recovery, with little fatigue and fewer than 1 symptom. None reported no improvement/worsening or met the CFS definition.
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - Retrospective study design (questionnaire); Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Baseline details only reported for whole study population. Participants who were admitted to hospital may have had a more severe illness than those who were managed as outpatients. Details obtained from medical records/notes which is heavily reliant on accurate/adequate documentation. ; Key confounders: Severity of symptoms; Group 1 Number missing: unclear, Reason: 2 participants were lost to follow-up, but unclear which intervention they received. Reported that outpatients were surveyed at a significantly longer interval from diagnosis than those admitted, but this is for study as a whole and is not reported separately for this population. ; Group 2 Number missing: unclear, Reason: 2 participants were lost to follow-up, but unclear which intervention they received. Reported that outpatients were surveyed at a significantly longer interval from diagnosis than those admitted, but this is for study as a whole and is not reported separately for this population.

- Actual outcome for young people - severity mixed or unclear: No improvement or worsening and meet CFS definition at mean 5.84 years (SD 2.07); Group 1: 0/5, Group 2: 0/3; Comments: The responses to each survey question were compared across the subject groups. A qualitative assessment of each subject's responses by a single investigator enabled allocation to one of the following groups: complete or near complete recovery, improvement but with ongoing symptoms, or no improvement or worse and likely to still meet the CDC definition for CFS.
All patients reported to have made a complete or near complete recovery, with little fatigue and fewer than 1 symptom. None reported no improvement/worsening or met the CFS definition.
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover -

	Low, Comments - Retrospective study design (questionnaire); Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Baseline details only reported for whole study population. Participants who were admitted to hospital may have had a more severe illness than those who were managed as outpatients. Details obtained from medical records/notes which is heavily reliant on accurate/adequate documentation. ; Key confounders: Severity of symptoms; Group 1 Number missing: unclear, Reason: 2 participants were lost to follow-up, but unclear which intervention they received. Reported that outpatients were surveyed at a significantly longer interval from diagnosis than those admitted, but this is for study as a whole and is not reported separately for this population. ; Group 2 Number missing: unclear, Reason: 2 participants were lost to follow-up, but unclear which intervention they received. Reported that outpatients were surveyed at a significantly longer interval from diagnosis than those admitted, but this is for study as a whole and is not reported separately for this population. Protocol outcome 2: Ability to resume occupation/school/study at longest follow up - Actual outcome for young people - severity mixed or unclear : Number who have "resumed normal activities" at mean 5.84 years (SD 2.07); Group 1: 5/5, Group 2: 3/3 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - Retrospective study design (questionnaire); Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Baseline details only reported for whole study population. Participants who were admitted to hospital may have had a more severe illness than those who were managed as outpatients. Details obtained from medical records/notes which is heavily reliant on accurate/adequate documentation. ; Key confounders: Severity of symptoms; Group 1 Number missing: unclear, Reason: 2 participants were lost to follow-up, but unclear which intervention they received. Reported that outpatients were surveyed at a significantly longer interval from diagnosis than those admitted, but this is for study as a whole and is not reported separately for this population. ; Group 2 Number missing: unclear, Reason: 2 participants were lost to follow-up, but unclear which intervention they received. Reported that outpatients were surveyed at a significantly longer interval from diagnosis than those admitted, but this is for study as a whole and is not reported separately for this population. - Actual outcome for young people - severity mixed or unclear : Number who attended school or work part-time for >2 years from diagnosis at mean 5.84 years (SD 2.07); Group 1: 0/5, Group 2: 0/3 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - Retrospective study design (questionnaire); Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Baseline details only reported for whole study population. Participants who were admitted to hospital may have had a more severe illness than those who were managed as outpatients. Details obtained from medical records/notes which is heavily reliant on accurate/adequate documentation; Key confounders: Severity of symptoms; Group 1 Number missing: unclear, Reason: 2 participants were lost to follow-up, but unclear which intervention they received. Reported that outpatients were surveyed at a significantly longer interval from diagnosis than those admitted, but this is for study as a whole and is not reported separately for this population. ; Group 2 Number missing: unclear, Reason: 2 participants were lost to follow-up, but unclear which intervention they received. Reported that outpatients were surveyed at a significantly longer interval from diagnosis than those admitted, but this is for study as a whole and is not reported separately for this population.
Protocol outcomes not reported by the study	Fatigue/fatiguability at longest follow up; Patient satisfaction at longest follow-up; Physical/cognitive functioning at longest follow up; Psychological status at longest follow up; Pain at longest follow up; Sleep quality at longest follow up;

Treatment-related adverse effects at longest follow up; Care needs at longest follow up; Impact on families/carers at longest follow up	

Appendix E Forest plots

E.1 Pre-diagnosis management strategies

E.1.1 Inpatient versus outpatient management

Figure 2: Quality of life: near or complete improvement in symptoms

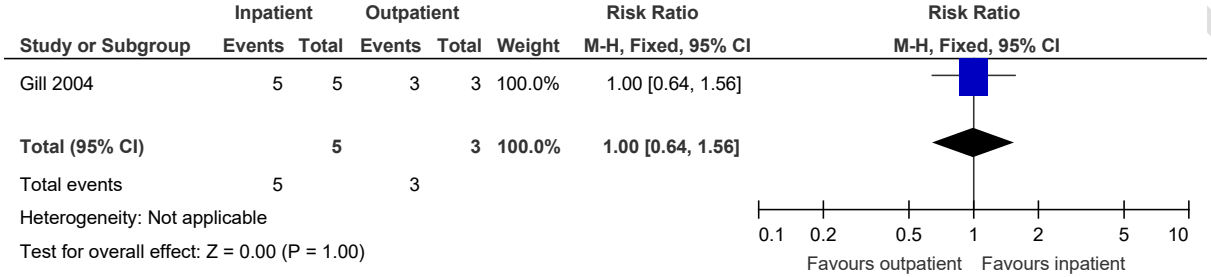


Figure 3: Quality of life: no improvement or worsening and meet CFS criteria

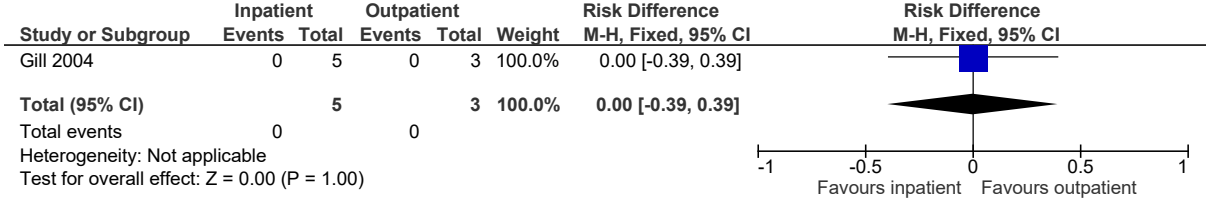


Figure 4: Ability to resume occupation/school/study: number who have resumed normal activities

Study or Subgroup	Inpatient Events	Inpatient Total	Outpatient Events	Outpatient Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gill 2004	5	5	3	3	100.0%	1.00 [0.64, 1.56]
Total (95% CI)		**5**		**3**	**100.0%**	**1.00 [0.64, 1.56]**
Total events	5		3			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.00 (P = 1.00)

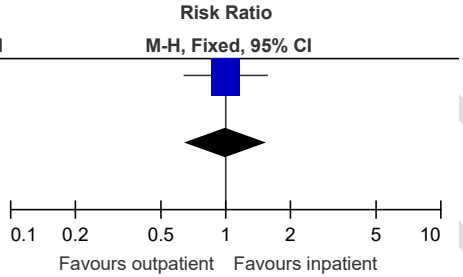
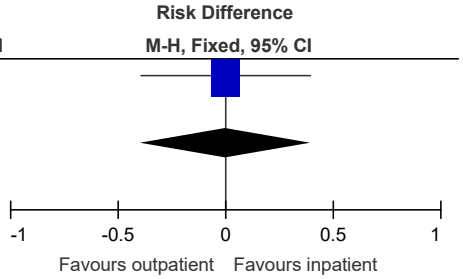


Figure 5: Ability to resume occupation/school/study: number who attended school or work part time for more than 2 years from diagnosis

Study or Subgroup	Inpatient Events	Inpatient Total	Outpatient Events	Outpatient Total	Weight	Risk Difference M-H, Fixed, 95% CI
Gill 2004	0	5	0	3	100.0%	0.00 [-0.39, 0.39]
Total (95% CI)		**5**		**3**	**100.0%**	**0.00 [-0.39, 0.39]**
Total events	0		0			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.00 (P = 1.00)



Appendix F GRADE tables

F.1 Pre-diagnosis management strategies

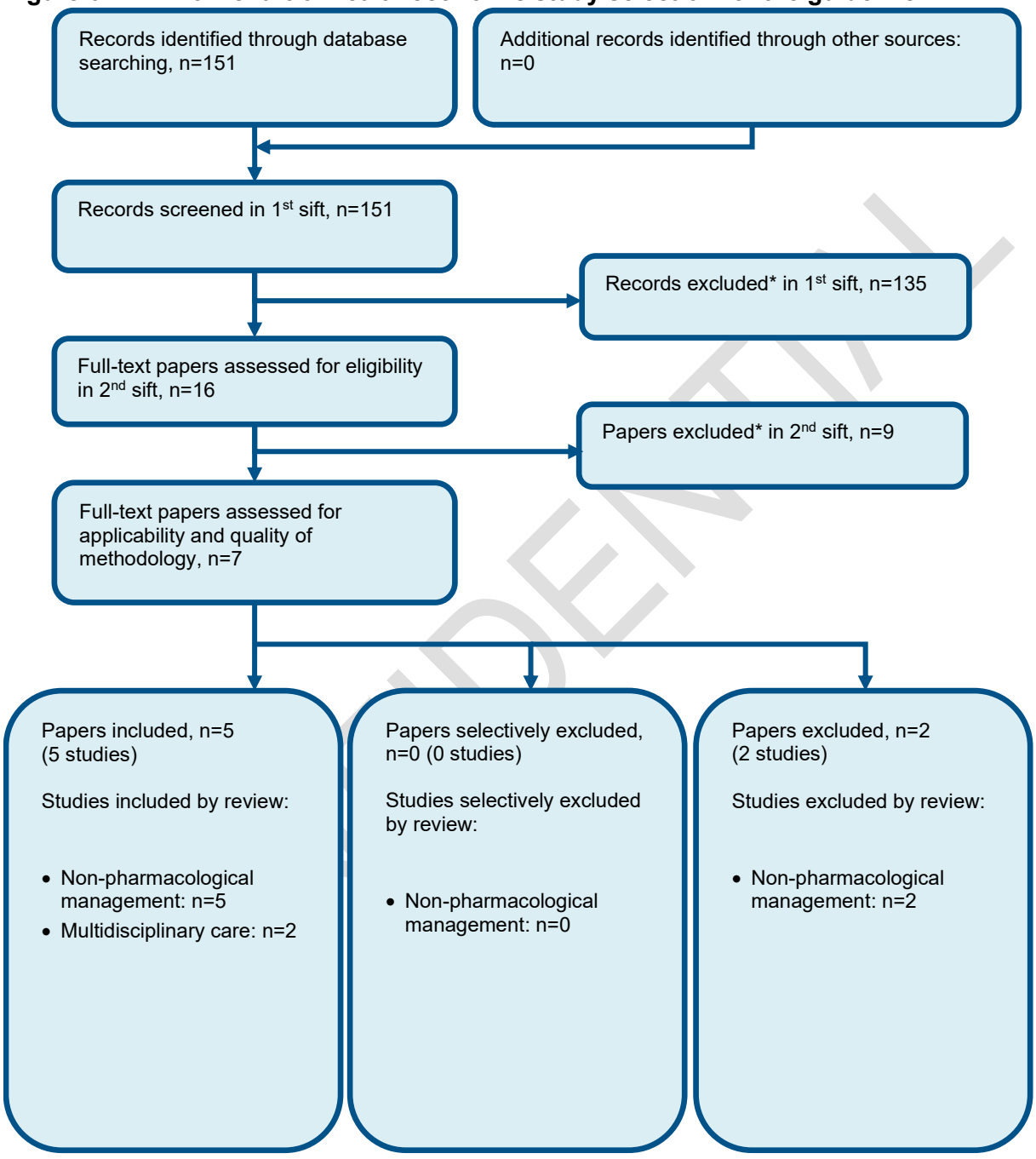
Table 7: Clinical evidence profile: inpatient versus outpatient management

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Inpatient versus outpatient management	Control	Relative (95% CI)	Absolute		
Quality of life: near or complete improvement (follow-up mean 5.84 years)												
1	observational studies	very serious[1]	no serious inconsistency	very serious[2]	very serious[3]	none	5/5 (100%)	100%	RR 1 (0.64 to 1.56)	0 fewer per 1000 (from 360 fewer to 560 more)	⊕OOO VERY LOW	CRITICAL
Quality of life: no improvement or worsening and meet CFS definition (follow-up mean 5.84 years)												
1	observational studies	very serious[1]	no serious inconsistency	very serious[2]	very serious[4]	none	0/5 (0%)	0%	RD 0 (-0.39 to 0.39)	0 fewer per 1000 (from 390 fewer to 390 more)	⊕OOO VERY LOW	CRITICAL
Ability to resume occupation/school/study: number who have resumed normal activities (follow-up mean 5.84 years)												
1	observational studies	very serious[1]	no serious inconsistency	very serious[2]	very serious[3]	none	5/5 (100%)	100%	RR 1 (0.64 to 1.56)	0 fewer per 1000 (from 360 fewer to 560 more)	⊕OOO VERY LOW	IMPORTANT
Ability to resume occupation/school/study: number who attended school or work part time for more than 2 years from diagnosis (follow-up mean 5.84 years)												
1	observational studies	very serious[1]	no serious inconsistency	very serious[2]	very serious[4]	none	0/5 (0%)	0%	RD 0 (-0.39 to 0.39)	0 fewer per 1000 (from 390 fewer to 390 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the majority of the evidence included an indirect population or by 2 increments if the majority of the evidence included a very indirect population. Downgraded by 2; 1) unclear if participants would have gone on to develop ME/CFS without intervention; 2) study used 1994 CDC criteria which does not include PEM as a compulsory feature
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs (MID = minimally important difference, see Methods Chapter of guideline for more information)
[4] Zero events in both arms - downgraded by 1 increment if the sample size is between 70 and 350, and downgraded by 2 increments if the sample size is less than70

Appendix G Economic evidence study selection

Figure 6: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

NB. Two papers were included in both the non-pharma and the multidisciplinary care reviews, in parallel with the review of clinical effectiveness.

Appendix H Economic evidence tables

None.

Appendix I Health economic model

No economic modelling was undertaken.

Appendix J Excluded studies

J.1 Pre-diagnosis management strategies

J.1.1 Clinical studies

Table 8: Studies excluded from the clinical review

Study	Exclusion reason
Aelfers 2013[8]	Study protocol
Akagi 2001[10]	Not review population (participants diagnosed with ME/CFS at the time of intervention); Incorrect study design (non-comparative study)
Ali 2017[11]	Not review population (participants had various 'functional somatic syndromes'); Incorrect study design (non-comparative study)
Anon 2010[180]	Incorrect study design (no intervention)
Anonymous 2012[17]	Abstract
Anonymous 2016[20]	Abstract of excluded study
Anonymous 2017[19]	Erratum to excluded study
Bakker 2011[28]	Not review population (unclear if participants were assessed for or went on to receive a diagnosis of ME/CFS)
Bazelmans 2005[36]	Not review population (participants diagnosed with ME/CFS at the time of intervention)
Behan 1990[39]	Not review population (participants diagnosed with post-viral fatigue syndrome at the time of intervention)
Behan 1990[40]	Incorrectly cited
Bethune 2003[44]	Incorrect study design (no intervention)
Bleijenberg 2009[46]	Trial registry record; not review population (participants diagnosed with ICF)
Bombardier 1996[49]	Incorrect study design (no intervention)
Bonner 1994[51]	Not review population (participants diagnosed with ME/CFS at the time of intervention); Incorrect study design (non-comparative study)
Candy 2004[77]	Not review population (unclear if participants were assessed for or went on to receive a diagnosis of ME/CFS)
Castro-Marrero 2016[84]	Not review population (participants diagnosed with ME/CFS at the time of intervention)
Chalder 1997[96]	Not review population (12% of participants diagnosed with ME/CFS at the time of intervention)
Chan 2013[98]	Not review population (participants diagnosed with CFS-like illness at the time of intervention)
Chan 2014[97]	Not review population (participants diagnosed with CFS-like illness at the time of intervention)
Chisholm 2001[103]	HE evaluation of excluded study (see record #117)
Cho 2009[104]	Not review population (participants with chronic fatigue >6 months, unclear if participants were assessed for or went on to receive a diagnosis of ME/CFS)
Collin 2017[111]	Incorrect study design (no intervention)
Comiskey 2010[120]	Incorrect study design (no intervention)

Study	Exclusion reason
Crawley 2011[132]	Incorrect study design (no intervention)
Crawley 2013[128]	Not review population (participants diagnosed with ME/CFS at the time of intervention)
Darbishire 2005[137]	Sub-analysis of excluded study
Dotsenko 2004[158]	Article not in English
Featherstone 1998[173]	Incorrect study design (qualitative study)
Friedberg 2013[182]	Not review population (participants diagnosed with unexplained chronic fatigue or CFS at the time of intervention)
Goodwin 2011[198]	Incorrect study design (no intervention)
Hall 1998[202]	Incorrect study design (no intervention)
Hall 2009[203]	Incorrect study design (webpage with information and patient feedback on mindfulness course)
Hamilton 2001[204]	Incorrect study design (no intervention)
Hana 1996[205]	Incorrect study design (no intervention)
Hartz 2003[208]	Not review population (participants diagnosed with ICF at the time of intervention)
Hartz 2004[207]	Not review population (participants diagnosed with ICF at the time of intervention)
Henderson 2014[218]	Not review population (participants diagnosed with ME/CFS at the time of intervention); Incorrect study design (non-comparative study)
Ho 2012[220]	Not review population (participants diagnosed chronic fatigue or CFS at the time of intervention)
Houghton 2011[223]	Not review population (participants with chronic fatigue >6 months, unclear if participants were assessed for or went on to receive a diagnosis of ME/CFS)
Huang 2010[224]	Incorrect study design (no intervention)
Huibers 2004[230]	Incorrect study design (no intervention)
Huibers 2004[229]	Incorrect study design (no intervention)
Huibers 2005[227]	Article not in English
Janse 2016[242]	Not review population (participants diagnosed with ICF at the time of intervention)
Jason 2000[250]	Incorrect study design (no intervention)
Jason 2011[249]	Incorrect study design (no intervention)
Khawaja 1998[263]	Not review population (participants diagnosed with ME/CFS at the time of intervention)
Kim 2013[265]	Not review population (participants diagnosed with ICF at the time of intervention)
Kim 2013[264]	Not review population (participants diagnosed with ICF at the time of intervention)
Kim 2015[266]	Not review population (participants diagnosed with CFS or ICF at the time of intervention)
King 1999[281]	Citation only
Knight 2013[283]	Incorrect study design (no intervention)
Krilov 1998[294]	Not review population (unclear if participants were assessed for or went on to receive a diagnosis of ME/CFS); Incorrect study design (non-comparative study)

Study	Exclusion reason
Lee 2015[302]	Not review population (participants diagnosed with ICF at the time of intervention)
Leone 2006[303]	Not review population (unclear if participants were assessed for or went on to receive a diagnosis of ME/CFS)
Malaguarnera 2008[324]	Not review population (elderly people with chronic fatigue)
Malik 2020 [325]	Not review population (some participants met diagnostic criteria for ME/CFS at baseline)
Marques 2017[326]	Not review population (participants diagnosed with ICF at the time of intervention)
Mehta 1995[340]	Incorrect study design (n=1 case study)
Meng 2014[342]	Not review population (participants with chronic fatigue >6 months, unclear if participants were assessed for or went on to receive a diagnosis of ME/CFS)
Moss-Morris 2011[354]	Incorrect study design (no intervention)
O'Dowd 2020[379]	Not review population (participants with fatigue 1-4 months, unclear if participants went on to receive a diagnosis of ME/CFS)
Patel 2003[394]	Not review population (participants diagnosed with ME/CFS at the time of intervention); Incorrect study design (non-comparative study)
Pheley 1999[409]	Incorrect study design (no intervention)
Prins 2004[417]	Sub-analysis of excluded study
Puetz 2008[419]	Not review population (participants with persistent fatigue, unclear if participants were assessed for or went on to receive a diagnosis of ME/CFS)
Ridsdale 2001[430]	Not review population (28% of participants diagnosed with ME/CFS at the time of intervention)
Ridsdale 2004[429]	Not review population (29% of participants diagnosed with ME/CFS at the time of intervention)
Ridsdale 2012[431]	Not review population (unclear if participants were assessed for or went on to receive a diagnosis of ME/CFS)
Russo 1998[444]	Incorrect study design (no intervention)
Sabes-Figuera 2012[445]	HE evaluation of excluded study (see record #257)
Saidi 2006[446]	Incorrect study design (no intervention)
Sankey 2006[447]	Not review population (participants diagnosed with ME/CFS at the time of intervention); Incorrect study design (non-comparative study)
Schmaling 2003[454]	Incorrect study design (no intervention)
Sharpe 1992[463]	Incorrect study design (no intervention)
Skapinakis 2003[467]	Incorrect study design (no intervention)
Stubhaug 2008[487]	Not review population (majority of participants diagnosed with ME/CFS at the time of intervention)
Tiev 1999[518]	Article not in English
Toussaint 2012[521]	Not review population (participants diagnosed with fibromyalgia, chronic fatigue and/or CFS)
Unger 2017[531]	Incorrect study design (no intervention)
Vermeulen 2006[547]	Not review population (participants diagnosed with ME/CFS at the time of intervention); Incorrect study design (non-comparative study)

Study	Exclusion reason
Westendorp 2016[566]	Not review population (participants had severe chronic pain or chronic fatigue); Incorrect study design (non-comparative study)
White 2001[570]	Incorrect study design (no intervention)

A call for evidence was sent out for three review questions for which the committee anticipated that there would be limited published evidence. Some articles were submitted with a clear indication of which of the three review questions they related to, but for many there was no clear indication. Regardless, all articles were assessed for eligibility for inclusion in all three reviews and one main table was created for all studies/articles submitted that were subsequently excluded. For some articles, there were multiple reasons for exclusion across the three review questions. The exclusion reason listed is the main reason for exclusion from the review that the article was judged to be most relevant to. For example, a quantitative study on the effectiveness of an intervention in people diagnosed with ME/CFS was considered to be most relevant to the experiences of interventions question, but the review protocol specified only qualitative studies to be included, so the main reason for exclusion would be incorrect study design. Some articles were relevant to the guideline in general but did not specifically attempt to answer any of the three review questions.

Table 9: Studies excluded from call for evidence

Study	Exclusion reason
Action for ME 2001[2]	Incorrect study design (quantitative survey)
Action for ME 2014[395]	No relevant themes
Action for ME 2019 Results from our big survey[1] (unpublished)	Incorrect study design (quantitative survey)
Action for ME and Association of Young People with ME (UK) 2008[3]	Incorrect study design (qualitative survey)
Adamowicz 2014[4]	Systematic review with different PICO
Adamson[5] (unpublished)	Incorrect study design (cohort)
Adedeji 2012[6]	Study/article does not address any of the call for evidence review questions
Adelakun[7]	No useable data - qualitative data reported as most frequently occurring words
Ahmed 2020[9]	Incorrect study design (systematic review; no qualitative data)
All-Party Parliamentary Group on ME 2010[12]	Not a qualitative study
Allwright 2019[13]	No relevant themes
Anderson 1997[15]	Mixed method study design with no extractable themes
Anderson[14] (unpublished)	Not review population (people already diagnosed with ME/CFS); Incorrect study design (qualitative)
Anon[491]	Incorrect study design (quantitative survey)
Anon[457]	Incorrect study design (non-comparative intervention study)
Anon[16]	Incorrect study design (non-comparative intervention study with quantitative outcomes)
Anon 2013[396] (unpublished)	Incorrect study design (quantitative survey)
Anon 2015[109]	Trial registry record; no results posted
Anon 2015[458]	Incorrect study design (quantitative)

Study	Exclusion reason
Anon 2015[18]	Unable to obtain
Anon 2016[34] (unpublished)	Letter/commentary/expert opinion
Anon 2016[425]	Study/article does not address any of the call for evidence review questions
Anon 2017[169]	Study/article does not address any of the call for evidence review questions
Anon 2018[414]	Not research article
Antcliff 2019[21]	Incorrect population (HCPs)
Antiel 2011[22]	Incorrect interventions (no intervention)
Armstrong 2012[23]	Study/article does not address any of the call for evidence review questions
Arnold 2015[24]	Incorrect study design (RCT)
Ates 2016[25]	Study/article does not address any of the call for evidence review questions
Augusto 2018[26]	Study/article does not address any of the call for evidence review questions
BACME 2019[27]	Incorrect population (survey of 'CFS/ME' services)
Balaguru 2012[29]	Study/article does not address any of the call for evidence review questions
Baos 2019[30]	RCT protocol
Baraniuk 2017[32]	Study/article does not address any of the call for evidence review questions
Baraniuk 2018[31]	Study/article does not address any of the call for evidence review questions (BMJ best practice)
Barnden 2016[33]	Study/article does not address any of the call for evidence review questions
Bazelmans 2004[35]	Incorrect population (therapists)
Bazelmans 2005[36]	Incorrect study design (quantitative)
Bazilevskaya 2006[37]	Study/article does not address any of the call for evidence review questions
Beasant[38] (unpublished)	Not review population (people already diagnosed with ME/CFS); Incorrect study design (qualitative)
Belgian Ministry of Social Affairs, Public Health and Environment 2000[41]	Guidelines including systematic review of the evidence (unclear source of data on patient experience of CBT)
Bell 2016[42]	Letter/commentary/expert opinion
Berkovitz 2009[43]	Incorrect interventions (no intervention)
Blease 2017[45]	Incorrect study design (review article)
Bloot 2015[47]	Incorrect study design (quantitative)
Blue Ribbon for the Awareness of Myalgic Encephalomyelitis 2010[48] (unpublished)	Incorrect study design (quantitative survey; no qualitative data)
Boneva 2019[50]	Incorrect interventions (no intervention)
Bould 2011[53]	Narrative review
Bould 2013[52]	Not relevant to any call for evidence questions

Study	Exclusion reason
Bowers 2019[54]	Study/article does not address any of the call for evidence review questions
Brigden 2018[57]	No intervention
Brigden 2018[55]	No relevant themes
Brigden 2016[56]	RCT protocol
Brigden[58] (unpublished)	Not review population (people already diagnosed with ME/CFS); Incorrect study design (qualitative)
Bringsli 2014[59]	Incorrect study design (quantitative survey)
Bristol CFS/ME Service[60] (unpublished)	Not review population (people already diagnosed with ME/CFS); Incorrect study design (qualitative)
Bristol CFS/ME Service[372]	Not review population (people already diagnosed with ME/CFS); Incorrect study design (qualitative)
Britain 2019[61]	Conference abstract
Brooks 2011[62]	Incorrect study design (quantitative)
Broughton 2017[63]	Incorrect interventions (specialist services rather than specific interventions)
Brouwers 2002[64]	Incorrect study design (RCT)
Brown 2012[66]	Study/article does not address any of the call for evidence review questions
Brown 2005[67]	Study/article does not address any of the call for evidence review questions
Brown 2015[65]	Study/article does not address any of the call for evidence review questions
Buchachenko 2013[72]	Study/article does not address any of the call for evidence review questions
Buchachenko 2005[70]	Study/article does not address any of the call for evidence review questions
Buchachenko 2006[71]	Study/article does not address any of the call for evidence review questions
Buchachenko 2017[69]	Study/article does not address any of the call for evidence review questions
Buchachenko 2019[68]	Study/article does not address any of the call for evidence review questions
Burgess 2012[73]	Incorrect study design (RCT)
Burke 1986[74]	Study/article does not address any of the call for evidence review questions
Butland 1982[75]	Study/article does not address any of the call for evidence review questions
Calello 2018[76]	Study/article does not address any of the call for evidence review questions
Carpenter 2013[78]	Study/article does not address any of the call for evidence review questions
Carruthers 2011[81]	Study/article does not address any of the call for evidence review questions
Carruthers 2012[80]	Study/article does not address any of the call for evidence review questions
Carruthers 2003[79]	Guidelines

Study	Exclusion reason
Casanova 2011[82]	Study/article does not address any of the call for evidence review questions
Castro-Marrero 2016[84]	Incorrect study design (RCT)
Castro-Marrero 2017[83]	Study/article does not address any of the call for evidence review questions
Cella 2011[86]	Incorrect study design (quantitative)
Cella 2011[85]	Incorrect study design (quantitative)
Centers for Disease Control and Prevention 2019[87]	Study/article does not address any of the call for evidence review questions
CFS/ME National Outcomes Database Team 2016[88]	Incorrect study design (non-comparative observational study)
CFS/ME Service for South Yorkshire and North Derbyshire 2019[89]	Incorrect study design (quantitative survey)
CFS/ME Service for South Yorkshire and North Derbyshire[90]	Incorrect study design (quantitative survey)
CFS/ME Working Group 2002[91] (unpublished)	No relevant themes
Chaudhuri 2003[101]	Study/article does not address any of the call for evidence review questions
Chalder 1993[93]	Study/article does not address any of the call for evidence review questions
Chalder 2010[94]	Incorrect study design (RCT)
Chalder 2010[92]	Incorrect study design (review, not qualitative)
Chalder 2015[95]	Incorrect study design (quantitative)
Chan 2019[99]	Not a qualitative study
Chang 2012[100]	Incorrect interventions (no intervention)
Childs 2019[102]	Incorrect study design (quantitative survey); no qualitative data
Chu 2018[105]	Study/article does not address any of the call for evidence review questions
Claypoole 2007[106]	Incorrect interventions (no intervention)
Cleare 2004[107]	Incorrect study design (quantitative)
Cliff 2019[108]	Study/article does not address any of the call for evidence review questions
Cockshell 2010[110]	Incorrect interventions (no intervention)
Collin 2018[115]	Study/article does not address any of the call for evidence review questions
Collin 2017[113]	Incorrect study design (non-comparative cohort study)
Collin 2017[111]	Incorrect study design (case-control)
Collin 2017[112]	Study/article does not address any of the call for evidence review questions
Collin 2016[116]	Study/article does not address any of the call for evidence review questions
Collin 2015[117]	Study/article does not address any of the call for evidence review questions
Collin 2012[118]	Incorrect study design (quantitative survey)

Study	Exclusion reason
Collin 2011[114]	Study/article does not address any of the call for evidence review questions
Comhaire 2018[119]	Incorrect study design (quantitative)
Cook 2017[121]	Incorrect interventions (no intervention)
Cooper 2019[122]	No relevant themes (qualitative data on an ME/CFS service, not specific interventions)
Corsius 2019[123]	Report summary; full report in Dutch
Costa 1995[124]	Study/article does not address any of the call for evidence review questions
Crawford 2010[126]	Study/article does not address any of the call for evidence review questions
Crawford 2012[125]	Letter/commentary/expert opinion
Crawford 2012[127]	Study advertisement
Crawley 2018[133]	Not relevant to monitoring/review question
Crawley 2013[130]	Incorrect interventions
Crawley 2013[128]	No relevant outcomes
Crawley 2011[132]	No intervention
Crawley 2009[129]	Study/article does not address any of the call for evidence review questions
Crawley 2009[131]	Study/article does not address any of the call for evidence review questions
Crowhurst 2005[134]	Letter/commentary/expert opinion
Crowhurst 2007[135]	No relevant themes
Currell[136]	No relevant themes (qualitative data on a specialist service, not specific interventions)
DARPA 2017[138]	Study/article does not address any of the call for evidence review questions
Davenport 2010[143]	Incorrect study design (conceptual model; not qualitative)
Davenport 2019[139]	Study/article does not address any of the call for evidence review questions
Davenport 2011[141]	Study/article does not address any of the call for evidence review questions
Davenport 2011[140]	Incorrect study design (quantitative)
Davenport 2019[142]	Letter/commentary/expert opinion
Davies 2008[144]	Study/article does not address any of the call for evidence review questions
Dawes 2019[170]	Executive summary of an excluded survey
Deale 2001[152]	Incorrect study design (RCT)
Deale 1998[151]	Incorrect study design (quantitative)
Deale 1997[150]	Incorrect study design (RCT)
De Becker 2000[146]	Study/article does not address any of the call for evidence review questions
De Becker 2001[145]	Study/article does not address any of the call for evidence review questions
de Carvalho 2011[147]	Study/article does not address any of the call for evidence review questions

Study	Exclusion reason
Deftereos 2016[153]	Incorrect population (expert clinicians)
de Lange 2008[148]	Incorrect study design (quantitative)
DeLuca 2004[154]	Incorrect interventions (no intervention)
de Vega 2017[149]	Study/article does not address any of the call for evidence review questions
Devasahayam 2012[155]	Study/article does not address any of the call for evidence review questions
Diao 2017[156]	Study/article does not address any of the call for evidence review questions
Dobson 2007[157]	Study/article does not address any of the call for evidence review questions
Dougall 2014[159]	Incorrect study design (RCT)
Doukrou 2019[160]	Incorrect study design (no qualitative data)
Dowsett 1997[161]	Study/article does not address any of the call for evidence review questions
Duyn 2017[162]	Study/article does not address any of the call for evidence review questions
Dyda 2018[163]	Study/article does not address any of the call for evidence review questions
Effective Health Care Program: Agency for Healthcare Research and Quality[164]	Systematic review protocol
Emerge Australia 2018[165]	Incorrect study design (quantitative survey)
Emerge Australia 2019[166]	Incorrect study design (quantitative survey)
Encephalitis Society 2017[167]	Study/article does not address any of the call for evidence review questions (website information)
Eroshenko 2004[168]	Study/article does not address any of the call for evidence review questions
Falk Hvidberg 2015[171]	Incorrect interventions (no intervention)
Faulkner 2016[172]	Letter/commentary/expert opinion
Fisher 2013[174]	No relevant themes
Fisk 1994[175]	Not relevant to any call for evidence questions
Flo 2014[176]	Incorrect study design (quantitative)
Fluge 2019[178]	Incorrect study design (RCT)
Fluge 2015[179]	Incorrect study design (quantitative)
Fluge 2016[177]	Study/article does not address any of the call for evidence review questions
Forward ME Survey 2019[385]	Not review population (people already diagnosed with ME/CFS); Incorrect study design (survey)
Franklin 2018[181]	Incorrect study design (quantitative)
Fukuda 2016[183]	Incorrect study design (RCT)
Garner 2019[184]	Study/article does not address any of the call for evidence review questions
Geraghty 2018[188]	Incorrect study design (narrative review)
Geraghty 2016[190]	Incorrect study design (debate article)
Geraghty 2019[189]	Incorrect study design (literature review)

Study	Exclusion reason
Geraghty 2019[186]	Letter/commentary/expert opinion
Geraghty 2017[185]	Incorrect study design (analysis of quantitative survey data)
Geraghty 2019[187]	Study/article does not address any of the call for evidence review questions
Ghatineh 2017[191]	Review of an RCT
Gielissen 2007[192]	Study/article does not address any of the call for evidence review questions
Gieré 2016[193]	Study/article does not address any of the call for evidence review questions
Gilder 2018[194]	Study/article does not address any of the call for evidence review questions
Gladwell 2013[196]	Not review population (people already diagnosed with ME/CFS); Incorrect study design (qualitative)
Goedendorp 2009[197]	Study/article does not address any of the call for evidence review questions
Haig-Ferguson 2019[199]	No relevant themes
Haig-Ferguson 2009[200]	No relevant themes
Halapy 2017[201]	Letter/commentary/expert opinion
Harada 1999[206]	Study/article does not address any of the call for evidence review questions
Haywood 2012[210]	Study/article does not address any of the call for evidence review questions
Haywood 2014[209]	Systematic review with different PICO
Heald 2019[211]	Study/article does not address any of the call for evidence review questions
Healthwatch Trafford 2017[213]	No relevant themes
Healthwatch Lancashire 2017[212]	Different focus to review question
Heins 2013[215]	Incorrect study design (quantitative)
Heins 2013[214]	Incorrect study design (quantitative)
Heins 2011[216]	Incorrect study design (quantitative)
Heins 2010[217]	Incorrect study design (quantitative)
Hives 2017[219]	Incorrect study design (diagnostic accuracy study)
Hodges 2018[221]	Incorrect interventions (no intervention)
Holtzman 2019[222]	Study/article does not address any of the call for evidence review questions
Hughes 2002[226]	Review article
Hughes 2018[225]	Study/article does not address any of the call for evidence review questions
Huibers 2004[228]	Incorrect population (some met criteria for CFS, some did not and results not reported separately
Ickmans 2014[231]	Incorrect interventions (no intervention)
ICNIRP Project Group 2017[232]	Study/article does not address any of the call for evidence review questions
Ingman 2016[235]	Incorrect study design (quantitative)

Study	Exclusion reason
Ingman[234]	Unable to obtain
Ingman[233]	Unable to obtain
Institute of Medicine 2015[236]	Study/article does not address any of the call for evidence review questions
ISRCTN Registry 2015[237]	Study/article does not address any of the call for evidence review questions
Jackson 2012[238]	Study/article does not address any of the call for evidence review questions
Janse 2019[239]	Prognostic study looking at predictors of outcome of CBT - none relevant to CFE questions
Janse 2019[241]	Incorrect study design (non-randomised quantitative study)
Janse 2018[243]	Incorrect study design (RCT)
Janse 2017[240]	Incorrect study design (RCT)
Janse 2016[242]	Incorrect population (idiopathic chronic fatigue); incorrect study design (RCT)
Janse 2015[244]	RCT protocol
Jason 2006[246]	Study/article does not address any of the call for evidence review questions
Jason 2008[251]	Study/article does not address any of the call for evidence review questions
Jason 2009[245]	Incorrect study design (quantitative)
Jason 2009[247]	Study/article does not address any of the call for evidence review questions
Jason 2015[252]	Review article
Jason 2018[248]	Not relevant to any call for evidence question
Jelinek 2001[253]	Study/article does not address any of the call for evidence review questions
Jenkins 2005[254]	Study/article does not address any of the call for evidence review questions
Jones 2012[255]	Incorrect study design (quantitative)
Josev 2019[256]	Incorrect interventions (no intervention)
Juutilainen 2018[257]	Study/article does not address any of the call for evidence review questions
Kapitein 2015[258]	Study/article does not address any of the call for evidence review questions
Kasevich 2002[259]	Study/article does not address any of the call for evidence review questions
Keller 2014[260]	Incorrect interventions (no intervention)
Kempke 2013[261]	Study/article does not address any of the call for evidence review questions
Kenyon 2019[262]	Incorrect study design (quantitative)
Kim 2019[267]	Study/article does not address any of the call for evidence review questions
Kindlon 2011[275]	Letter/commentary/expert opinion
Kindlon 2017[269]	Letter/commentary/expert opinion
Kindlon 2009[268]	Letter/commentary/expert opinion
Kindlon 2010[277]	Letter/commentary/expert opinion

Study	Exclusion reason
Kindlon 2010[279]	Letter/commentary/expert opinion
Kindlon 2011[271]	Letter/commentary/expert opinion
Kindlon 2012[272]	Letter/commentary/expert opinion
Kindlon 2012[273]	Letter/commentary/expert opinion
Kindlon 2015[270]	Letter/commentary/expert opinion
Kindlon 2015[278]	Letter/commentary/expert opinion
Kindlon 2015[280]	Letter/commentary/expert opinion
Kindlon 2011[274]	Letter/commentary/expert opinion
Kindlon 2009[276]	Letter/commentary/expert opinion
Kingdon 2018[282]	Study/article does not address any of the call for evidence review questions
Knoester 2019[284]	Study/article does not address any of the call for evidence review questions
Knoop 2008[289]	Incorrect study design (RCT)
Knoop 2007[288]	Incorrect study design (quantitative)
Knoop 2007[286]	Incorrect study design (quantitative)
Knoop 2007[285]	Incorrect study design (quantitative)
Knoop 2008[287]	Incorrect study design (RCT)
Knudsen 2011[290]	Study/article does not address any of the call for evidence review questions
Kodama 2013[291]	Study/article does not address any of the call for evidence review questions
Kreyberg 2007[292]	Guidelines
Kreyberg 2007[293]	Incorrect population (nursing staff)
Lacerda 2018[295]	Study/article does not address any of the call for evidence review questions
Lacerda 2019[296]	No relevant themes
LaManca 1998[297]	Incorrect interventions (no intervention)
Lapp 2019[298]	Letter/commentary/expert opinion
Larun 2014[299]	Incorrect study design (systematic review of RCTs)
Leaman 1997[300]	Study/article does not address any of the call for evidence review questions
Leone 2006[304]	Not relevant to any call for evidence question
Lewis 2013[305]	Incorrect interventions (no intervention)
Lien 2019[306]	Study/article does not address any of the call for evidence review questions
Light 2009[307]	Incorrect study design (quantitative)
Lincolnshire Partnership 2019[308]	Qualitative data in the form of quotes - no thematic analysis
Liu 2018[309]	Study/article does not address any of the call for evidence review questions
Lloyd 2012[311]	Incorrect study design (quantitative)
Lloyd 2012[310]	Incorrect study design (RCT)
Loades 2016[315]	Systematic review with different PICO

Study	Exclusion reason
Loades 2019[312] (unpublished)	Incorrect population (already diagnosed with ME/CFS); incorrect study design (cross-sectional epidemiological study with no interventions)
Loades 2019[316]	Incorrect study design (qualitative); also excluded from experiences of interventions review due incorrect population (healthcare professionals)
Loades 2019[313]	Incorrect study design (quantitative)
Loades 2018[314]	Study/article does not address any of the call for evidence review questions
Loy 2016[317]	Incorrect study design (quantitative)
Lyshevski 2001[318]	Study/article does not address any of the call for evidence review questions
Maes 2006[321]	Study/article does not address any of the call for evidence review questions
Maes 2009[322]	Study/article does not address any of the call for evidence review questions
Maes 2012[323]	Study/article does not address any of the call for evidence review questions
Marshall 1997[327]	Not relevant to any call for evidence question
Marshall 1996[328]	Incorrect study design (quantitative)
Mathew 2009[329]	Study/article does not address any of the call for evidence review questions
May 2010[330]	Study/article does not address any of the call for evidence review questions
McCourt 2019[331]	Study/article does not address any of the call for evidence review questions
McDermott 2006[332]	Study/article does not address any of the call for evidence review questions
McGregor 2016[333]	Study/article does not address any of the call for evidence review questions
McGregor 2019[334]	Study/article does not address any of the call for evidence review questions
McManimen 2016[336]	Study/article does not address any of the call for evidence review questions
McManimen 2019[335]	Not review population (people already diagnosed with ME/CFS); Incorrect study design (qualitative)
McPhee 2019[337]	Qualitative section was related to information given to patients about possible harms, data about harm was quantitative
ME Action 2019[301]	Not review population (people already diagnosed with ME/CFS); Incorrect study design (survey)
ME/cvs Vereniging 2016[338]	Report summary; full report in Dutch
Meeus 2015[339]	Incorrect study design (RCT)
ME Group 2019[320]	No qualitative findings/data analysis reported
ME Group 2014[319]	No qualitative findings/data analysis reported
Melamed 2019[341]	Study/article does not address any of the call for evidence review questions
Mihelicova 2016[343]	Study/article does not address any of the call for evidence review questions

Study	Exclusion reason
Miller 2015[344]	Study/article does not address any of the call for evidence review questions
Millions Missing Canada 2017[345]	Incorrect study design (quantitative survey)
Missen 2012[346]	No relevant outcomes
Moneghetti 2018[347]	Incorrect interventions (no intervention)
Montoya 2018[348]	Incorrect study design (RCT)
Montoya 2013[349]	Incorrect study design (RCT)
Moore 2000[350]	Study/article does not address any of the call for evidence review questions
Moore 2015[351]	Study/article does not address any of the call for evidence review questions
Morens 2019[352]	Study/article does not address any of the call for evidence review questions
Morris 2014[353]	Study/article does not address any of the call for evidence review questions
Murdock 2017[355]	Study/article does not address any of the call for evidence review questions
Myalgic Encephalomyelitis / Chronic Fatigue Syndrome Advisory Committee 2019[356]	Study/article does not address any of the call for evidence review questions
Nacul 2011[359]	Study/article does not address any of the call for evidence review questions
Nacul 2011[360]	Study/article does not address any of the call for evidence review questions
Nacul 2018[361]	Study/article does not address any of the call for evidence review questions
Nacul 2019[358]	Study/article does not address any of the call for evidence review questions
Nacul 2019[357]	Study/article does not address any of the call for evidence review questions
Nagy-Szakal 2018[362]	Study/article does not address any of the call for evidence review questions
Natelson 2017[364]	Study/article does not address any of the call for evidence review questions
Natelson 2017[363]	Study/article does not address any of the call for evidence review questions
National Centers for Environmental Information[365]	Study/article does not address any of the call for evidence review questions
National Collaborating Centre for Primary Care 2007[366]	Study/article does not address any of the call for evidence review questions
Naviaux 2016[369]	Study/article does not address any of the call for evidence review questions
Naviaux 2017[368]	Study/article does not address any of the call for evidence review questions
Newberry 2018[370]	Study/article does not address any of the call for evidence review questions
Newton 2010[371]	Study/article does not address any of the call for evidence review questions

Study	Exclusion reason
NHS North Bristol 2019[372]	No relevant themes (qualitative data on specialist services, not specific interventions)
Nijhof 2014[376]	Incorrect study design (quantitative)
Nijhof 2013[375]	Incorrect study design (quantitative)
Nijhof 2012[373]	Incorrect study design (RCT)
Nijhof 2011[374]	RCT protocol
Norfolk and Suffolk Service 2009[377]	Unable to obtain (web link unavailable)
Norris 2017[378]	Incorrect study design (cross-sectional analysis of quantitative data)
Ocon 2012[380]	Study/article does not address any of the call for evidence review questions
Odoom 2018[381]	Study/article does not address any of the call for evidence review questions
Office for National Statistics 2018[382]	Not relevant to any call for evidence questions
Ojo-Amaize 1994[383]	Study/article does not address any of the call for evidence review questions
Oliver 2018[384]	Incorrect study design (quantitative survey)
PACE Trial participant dataset[386]	Study/article does not address any of the call for evidence review questions
Packer 1997[387]	Study/article does not address any of the call for evidence review questions
Pakpoor 2017[388]	Study/article does not address any of the call for evidence review questions
Parslow 2018[390]	No relevant themes
Parslow 2017[392]	Incorrect study design (qualitative)
Parslow 2017[391]	Systematic review with different PICO
Parslow 2015[389]	Incorrect study design (qualitative; assessed for monitoring and review question)
Pastula 2014[393]	Study/article does not address any of the call for evidence review questions
Patrick Neary 2008[397]	Incorrect interventions (no intervention)
Peci 2015[398]	Study/article does not address any of the call for evidence review questions
Peckerman 2003[399]	Study/article does not address any of the call for evidence review questions
Pemberton 2014[401]	No relevant themes
Pemberton 2014[400]	No relevant themes
Peterson 1991[406]	Not relevant to any call for evidence question
Peterson 1994[407]	Incorrect interventions (no intervention)
Perrin 1993[403]	Review; study/article does not address any of the call for evidence review questions
Perrin 1998[404]	Incorrect study design (non-randomised quantitative study)
Perrin 2011[405]	Incorrect study design (non-randomised quantitative study)
Pheby 2009[408]	Incorrect study design (survey) and no useable data

Study	Exclusion reason
Physios for M.E[410] (unpublished)	Not review population (people already diagnosed with ME/CFS); Incorrect study design (qualitative)
Plascencia-Villa 2016[411]	Study/article does not address any of the call for evidence review questions
Polli 2019[412]	Incorrect study design (quantitative)
Polo 2019[413]	Incorrect study design (no qualitative data)
Prins 2005[415]	Incorrect study design (quantitative)
Prins 2001[416]	Incorrect study design (RCT)
Prokhorov 2016[418]	Study/article does not address any of the call for evidence review questions
Puri 2011[420]	Incorrect study design (diagnostic accuracy study)
Quarmby 2007[421]	Incorrect study design (quantitative)
Raine 2004[422]	Incorrect population (GPs)
Rand Corporation[423]	Study/article does not address any of the call for evidence review questions
Rawlins 2008[424]	Study/article does not address any of the call for evidence review questions
Regland 2015[426]	Incorrect study design (quantitative)
Reynolds 2014[427]	Incorrect interventions (no intervention)
Richardson 2002[428]	Review article
Rimes 2014[432]	Incorrect study design (quantitative)
Roberts 2016[435]	Study/article does not address any of the call for evidence review questions
Roberts 2009[433]	Incorrect study design (quantitative)
Roberts 2018[434]	Study/article does not address any of the call for evidence review questions
Roe[436]	No relevant themes (qualitative data on a specialist service, not specific interventions)
Roerink 2017[439]	Study/article does not address any of the call for evidence review questions
Roerink 2017[437]	Incorrect study design (RCT)
Roerink 2015[438]	RCT protocol
Roma 2019[440]	Incorrect interventions (no intervention)
Rowe 2019[441]	Incorrect study design (questionnaire with closed and open ended questions; no thematic analysis)
Rowe 2017[442]	Review article
Ruggieri 2017[443]	Study/article does not address any of the call for evidence review questions
Santini 2018[448]	Study/article does not address any of the call for evidence review questions
Ŝarić 2016[449]	Study/article does not address any of the call for evidence review questions
Scheeres 2009[450]	Study/article does not address any of the call for evidence review questions
Scheeres 2008[452]	Incorrect study design (quantitative)
Scheeres 2008[451]	Incorrect study design (quantitative)

Study	Exclusion reason
Scheeres 2007[453]	Study/article does not address any of the call for evidence review questions
Schmaling 2019[455]	Study/article does not address any of the call for evidence review questions
Schweitzer 1995[456]	Not relevant to any call for evidence question
Severens 2004[459]	Letter/commentary/expert opinion
Shakespeare 2017[460]	Study/article does not address any of the call for evidence review questions
Shan 2018[461]	Study/article does not address any of the call for evidence review questions
Sharpe 1991[464]	Study/article does not address any of the call for evidence review questions
Sharpe 2015[462]	Incorrect study design (RCT)
Shukla 2015[465]	Incorrect study design (quantitative)
Shungu 2012[466]	Study/article does not address any of the call for evidence review questions
Smith 2014[469]	Incorrect study design (systematic review of RCTs)
Smith 2013[470]	Systematic review with different PICO
Smith 2015[468]	Incorrect study design (systematic review of RCTs)
Snell 2013[471]	Study/article does not address any of the call for evidence review questions
Snounou 2019[472]	Not review population (people already diagnosed with ME/CFS); Incorrect study design (qualitative)
Solomon-Moore 2019[473]	Incorrect study design (baseline cross-sectional data from an RCT)
Stahl 2014[474]	Incorrect study design (quantitative)
Staud 2017[476]	Incorrect study design (RCT)
Staud 2018[475]	Incorrect study design (quantitative)
Steffen 2002[477]	Study/article does not address any of the call for evidence review questions
Stevelink 2019[478]	Study/article does not address any of the call for evidence review questions
Stevens 2018[479]	Study/article does not address any of the call for evidence review questions
Stevens 2010[480]	Incorrect study design (case study)
Stoll 2017[481]	Systematic review with different PICO
Stordeur 2008[482]	Study/article does not address any of the call for evidence review questions
Strassheim 2018[483]	Study/article does not address any of the call for evidence review questions
Strawbridge 2019[484]	Not relevant to any call for evidence question
Strayer 2012[485]	Incorrect study design (RCT)
Strbak 2011[486]	Study/article does not address any of the call for evidence review questions
Stulemeijer 2005[488]	Incorrect study design (RCT)
Sumathipala 2008[489]	Incorrect population (medically unexplained symptoms)
Sunnquist 2018[490]	Incorrect study design (quantitative)

Study	Exclusion reason
Suvorov 1998[492]	Study/article does not address any of the call for evidence review questions
Swinscow 1997[493]	Study/article does not address any of the call for evidence review questions
Taylor 2004[496]	Incorrect study design (RCT)
Taylor 2019 Leeds and York CFS/ME Service[495] (unpublished)	No qualitative data
Taylor 2016[494]	Study/article does not address any of the call for evidence review questions
Teitelbaum 2001[497]	Incorrect study design (RCT)
Terzi 2016[498]	Study/article does not address any of the call for evidence review questions
The 2010[511]	Incorrect study design (RCT)
The 2007[512]	Incorrect study design (RCT)
The Consortium of Multiple Sclerosis Centers Health Services Research Subcommittee 1997[510]	Not relevant to any call for evidence questions
The 25% ME Group 2010[499]	Different focus to review question
The 25% ME Group 2014[500] (unpublished)	Report on a research presentation; no qualitative data from people with ME/CFS
The 25% ME Group 2004[509]	Incorrect study design (quantitative survey)
The 25% ME Group 2000[506]	Incorrect study design (quantitative survey)
The 25% ME Group 2001[501]	Incorrect study design (quantitative survey)
The 25% ME Group[508]	Article; no qualitative data from people with ME/CFS
The 25% ME Group 2002[505] (unpublished)	Incorrect study design (quantitative survey)
The 25% ME Group 2017[503]	Not relevant to any call for evidence questions
The 25% ME Group 2018[502]	Not relevant to any call for evidence questions
The 25% ME Group 2001[504]	Incorrect study design (quantitative survey)
The 25% ME Group 2016[507]	Study/article does not address any of the call for evidence review questions (newsletter)
The ME Association 2010[513]	Incorrect study design (quantitative survey)
The ME Association 2015[514]	Survey including quantitative and qualitative data, but no analysis on the qualitative data
The Neurological Alliance 2019[515]	Incorrect study design (quantitative survey)
Thomas 2009[516]	Incorrect interventions (no intervention)
Tiersky 2001[517]	Incorrect study design (quantitative)
Timbol 2019[519]	No relevant themes
Togo 2015[520]	Incorrect interventions (no intervention)
Trabal 2012[522]	Study/article does not address any of the call for evidence review questions
Tummers 2013[525]	Incorrect study design (quantitative)
Tummers 2012[524]	Incorrect study design (RCT)
Tummers 2010[523]	Incorrect study design (quantitative)

Study	Exclusion reason
Twisk 2014[530]	Letter/commentary/expert opinion
Twisk 2017[527]	Letter/commentary/expert opinion
Twisk 2018[526]	Report summary; full report in Dutch
Twisk 2015[529]	Study/article does not address any of the call for evidence review questions
Twisk 2015[528]	Incorrect study design (review article)
Van Campen 2018[532]	Incorrect interventions (no intervention)
Van Campen 2018[534]	Study/article does not address any of the call for evidence review questions
Van Campen 2019[533]	Incorrect study design (quantitative)
Van Den Eede 2011[535]	Study/article does not address any of the call for evidence review questions
Van Der Schaaf 2015[537]	RCT protocol
Van Der Schaaf 2017[536]	Study/article does not address any of the call for evidence review questions
Van Der Werf 2002[538]	Study/article does not address any of the call for evidence review questions
Van Konynenburg 2010[539]	Conference abstract
Van Kuppeveld 2010[540]	Study/article does not address any of the call for evidence review questions
VanNess 2007[541]	Incorrect interventions (no intervention)
VanNess 2010[542]	Incorrect intervention (exercise test)
Velleman 2016[543]	Incorrect population (siblings) and no relevant themes
Vercoulen 1996[545]	Incorrect study design (RCT)
Vercoulen 1996[544]	Study/article does not address any of the call for evidence review questions
Vermeulen 2010[546]	Study/article does not address any of the call for evidence review questions
Vermeulen 2014[548]	Study/article does not address any of the call for evidence review questions
Vernon 2004[549]	Unable to obtain
Verspaandonk 2015[550]	Incorrect study design (quantitative)
Vink 2017[551]	Incorrect study design (quantitative)
Vink 2018[554]	Review of an RCT
Vink 2018[553]	Incorrect study design (reanalysis of a Cochrane review); no qualitative data
Vink 2019[555]	Systematic review: references checked
Vink 2019[552]	Incorrect study design (reanalysis of a Cochrane review); no qualitative data
Wallis 2016[557]	Study/article does not address any of the call for evidence review questions
Wallis 2018[556]	Incorrect study design (quantitative)
Wang 2017[559]	Study/article does not address any of the call for evidence review questions
Watt 2012[560]	Incorrect study design (quantitative)

Study	Exclusion reason
Wearden 2006[563]	Study/article does not address any of the call for evidence review questions
Wearden 2010[561]	Incorrect study design (RCT)
Wearden 2013[562]	Incorrect study design (prognostic)
Webb 2011[564]	No relevant themes
Werbach 2000[565]	Incorrect study design (literature review)
White 2007[569]	RCT protocol
White 2011[568]	Incorrect study design (RCT)
White 2013[567]	Study/article does not address any of the call for evidence review questions
Whitehead 2009[571]	Study/article does not address any of the call for evidence review questions
Whitehead 2002[572]	Study/article does not address any of the call for evidence review questions
Wiborg 2010[574]	Incorrect study design (reanalysis of RCTs)
Wiborg 2014[576]	Incorrect study design (quantitative)
Wiborg 2015[575]	Incorrect study design (RCT)
Wiborg 2011[573]	Incorrect study design (quantitative)
Wieczorek 2017[558]	Study/article does not address any of the call for evidence review questions
Wilshire 2018[580]	Incorrect study design (reanalysis of an RCT)
Wilshire 2019[579]	Letter/commentary/expert opinion
Wilshire 2017[577]	Incorrect study design (critical commentary and reanalysis of an RCT)
Wilshire 2017[578]	Letter/commentary/expert opinion
Worm-Smeitink 2019[582]	Incorrect study design (RCT)
Worm-Smeitink 2017[581]	Study/article does not address any of the call for evidence review questions
Worm-Smeitink 2016[583]	Incorrect study design (quantitative)
Yorkshire Fatigue Clinic [402]	Not review population (people already diagnosed with ME/CFS); Incorrect study design (survey)
Zablotskii 2016[584]	Study/article does not address any of the call for evidence review questions
Zablotskii 2018[585]	Study/article does not address any of the call for evidence review questions
Zhi 2017[586]	Study/article does not address any of the call for evidence review questions
Zielinski 2019[587]	Study/article does not address any of the call for evidence review questions

J.1.2 Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2003 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

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