Review protocol for pharmacological interventions

ID	Field	Content
	Scope	Management of ME/CFS
	Draft review question	3.1 What is the clinical and cost effectiveness of pharmacological interventions for people with ME/CFS?
0.	PROSPERO registration number	Not registered.
1.	Review title	What is the clinical and cost-effectiveness of pharmacological interventions for people with ME/CFS?
2.	Review question	What is the clinical effectiveness, cost-effectiveness and acceptability (including patient experiences) of pharmacological interventions for people with ME/CFS.
3.	Objective	Intervention review • To identify the most clinically and cost-effective pharmacological methods to improve outcomes in adults and children with a diagnosis of ME/CFS Qualitative review • To identify the experiences of people who have had pharmacological interventions for 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 • PsychInfo 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 diagnosed as having ME/CFS.

7.	Intervention/Exposure/Test
	
	(intervention review)
		Mode of delivery, dose and duration of drug treatment are not pre-specified in this protocol. This is partly because as there are no known drug liscenced fo use in ME/CFS we are interested in evaluating different drug parameters. Furthermore, because this question is intended to cover any pharmaceutical treatments evaluated by RCTs in this population, we cannot possibly list treatment parameters for all drugs we might encounter.
		
		These can include (but are not restricted to):
		
		• Antidepressants
		  ○ Include all SSRIs / SNRIs and tricyclics
		• Immunomodulatory drugs. For example:
		  ○ Rintatolimod (Ampligen)
		  ○ Rituximab
		• Pro-inflammatory cytokines. For example:
		  ○ Anakinra
		• Sleep medication. For example:
		  ○ Melatonin
		• Pain relief. For example:
		  ○ Pregabalin
		  ○ Gabapentin
		  ○ cannabinoids
		• Antiviral drugs
		• Oral corticosteroids
		  ○ fludrocortisone / hydrocortisone / other steroids
		• Modafinil
		• Sodium Valproate

		• Low dose Naltrexone
8.	Comparator/Reference standard/Confounding factors (intervention review)	• No treatment • Each other (both within and between classes) • Placebo/control/usual care
9.	Phenomena of interest (qualitative review)	The perceptions of people that have had pharmacological interventions for ME/CFS and about the benefits and harms they experienced.
11.	Types of study to be included	<u>Intervention review</u> • Randomised controlled trials • Systematic review of randomised controlled trials. For a systematic review to be included it must be conducted to the same methodological standard as NICE guideline reviews. If sufficient details are not provided to include a relevant systematic review, the review will be used for citation searching. Cross-over RCTs will be considered provided wash-out period is considered adequate. Non RCTs will not be considered as they will yield data that is at too high a risk of bias for decision-making <u>Qualitative review</u> Qualitative studies (e.g. transcript data collected from focus groups / semi structured interviews) and surveys
11.	Other exclusion criteria	Non-English language studies.

		Abstracts will be excluded as it is expected there will be sufficient full text published studies available.
12.	Context	N/A

13.	Primary outcomes (critical outcomes)	<u>Intervention review</u>
		Longest follow up available:
		
		CRITICAL OUTCOMES:
		• Mortality
		• Quality of life (any validated scales). For example:
		  o SF36
		  o EQ5D
		• General symptom scales (any validated scales). For example:
		  o De Paul Symptom Questionnaire
		  o Self Rated Clinical Global Impression Change Score
		• Fatigue/fatiguability (any validated scales). For example:
		  o Chalder fatigue Scale
		  o Fatigue Severity Scale
		  o Fatigue Impact scale
		• Physical functioning (any validated scales). For example:
		  o SF36 physical function
		  o SF36 PCS
		• Cognitive function (any validated scales). For example:
		  o MMSE
		• Psychological status (any validated scales). For example:
		  o Hospital Anxiety and Depression Scale
		  o Becks Depression Inventory
		• Pain (VAS/NRS)

		• Sleep quality (any validated scales). For example:
		  ○ Pittsburgh Sleep quality Index
		  ○ Epworth Sleepiness Scale
		  ○ Leeds Sleep Evaluation Questionnaire VAS
		• Treatment-related adverse effects
		• Activity levels – step counts
		• Return to school / work
		• Exercise performance measures. For example:
		  ○ Hand grip
		  ○ Maximal Cycle Exercise Capacity
		  ○ 6 min walk
		  ○ Timed Up and Go
		  ○ 5 repetition sit to stand
		  ○ 40m walk speed
		  ○ Step test
		
		<u>Qualitative review</u>
		Themes emerging from qualitative data

14.	Secondary outcomes (important outcomes)	<u>Intervention review</u> • Care needs • Impact on families and carers
15.	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.

		Intervention review 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. Qualitative review A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). A second reviewer will quality-assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary).
16.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For the intervention review 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) For the qualitative review the CASP qualitative checklist will be used to assess risk of bias of individual studies. 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking:

		• papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments 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.
17.	Strategy for data synthesis	<u>Intervention review</u> 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. Indirectness: 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%.

		The criteria used to diagnose people with CFS/ME should include post exertional malaise (PEM) as a compulsory feature. If the criteria does not include PEM the population will be downgraded for indirectness. 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. <u>Qualitative review</u> The synthesis of qualitative data will follow a thematic analysis approach. Information will be synthesised into main review findings. Results will be presented in a detailed narrative and in table format with summary statements of main review findings. GRADE CERQual will be used to synthesise the qualitative data and assess the certainty of evidence for each review finding.
18.	Analysis of sub-groups	<u>Stratification:</u> Age: children and young people vs adults Severity: severe vs moderate as defined by the studies Where populations are mixed/unclear, these will be analysed in mixed/unclear population strata.

		Subgroups to investigate if heterogeneity is present None		
19.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☒ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
20.	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.	Review team members	From the National Guideline Centre: • Dr Kate Kelley [Guideline lead] • Ms Maria Smyth [Senior systematic reviewer] • Ms Melina Vasileiou [Systematic reviewer]		

		• Dr Richard Clubbe [Systematic reviewer] • Dr Karin van Bart [Systematic reviewer] • Mr David Wonderling [Health economist] • Ms Agnes Cuyas [Information specialist] • Ms Kate Ashmore [Project manager]
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	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.
28.	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
29.	Other registration details	N/A
30.	Reference/URL for published protocol	N/A
31.	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.
32.	Keywords	
33.	Details of existing review of same topic by same authors	N/A
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	N/A
36.	Details of final publication	www.nice.org.uk