National Institute for Health and Care Excellence

Draft

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

[D] Evidence reviews for identifying and diagnosing ME/CFS

NICE guideline <number>

Evidence reviews underpinning recommendations and research recommendations in the NICE guideline

November 2020

Draft for Consultation

These evidence reviews were developed by National Guideline Centre

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Identifying and diagnosing ME/CFS

Review questions

1. In people with suspected ME/CFS, what are the criteria used to establish a diagnosis?
2. What is the diagnostic accuracy of specific tests to identify ME/CFS in people with suspected ME/CFS?
3. What are the predictive accuracies of specific clinical symptoms and signs to identify people who will subsequently be given a clinical diagnosis of ME/CFS?

Review questions

Key areas to be covered in the scope included identification and assessment before diagnosis and diagnosis of ME/CFS. This evidence report covers both areas of the scope.

ME/CFS affects people of all ages, races and socioeconomic groups. Discussion with the committee identified that the focus for identifying people with suspected ME/CFS and then diagnosing ME/CFS is clinical assessment. ME/CFS has historically been named and described in various ways. Names that have been used include: myalgic encephalomyelitis (ME), chronic fatigue syndrome (CFS), Post Viral Fatigue Syndrome (PVFS), Post Infection Fatigue Syndrome (PIFS), systemic exertion intolerance disease (SEID) and, combined names such as CFS/ME and ME/CFS. In the absence of a definitive test or biomarker, diagnosis has been mainly based on patterns of reported symptoms. Nevertheless, clinical descriptions of ME/CFS are variable, with each set of existing diagnostic criteria prioritising different symptoms as primary indicators, for example: factors such as fatigue, fatiguability, cognitive difficulties and the after-effects of exertion. The majority of diagnostic criteria to date have focussed on fatigue as the primary symptom, along with a combination of other symptoms. People with ME/CFS have queried this primary use of fatigue for diagnosis, and instead emphasise that the condition can include a breadth of symptoms affecting multiple systems and environmental intolerances which significantly reduce ability to function.

People with ME/CFS report delays in diagnosis, and research has highlighted that many healthcare professionals including GPs lack the confidence and knowledge to recognise, diagnose and manage ME/CFS. Delays in diagnosis can have an impact on the physical and emotional health of the person wating for a diagnosis. It is important to identify people with ME/CFS as early as possible to ensure they are given information to try to prevent worsening of symptoms and any further deterioration of health.

To inform the recommendations in the areas of identification and diagnosis of ME/CFS three review questions were conducted. The committee used these reviews to inform their recommendations in these areas.

1. Diagnostic criteria

1.1. Review question

In people with suspected ME/CFS, what are the criteria used to establish a diagnosis?

This review examines the criteria currently in use in clinical practice and research to assess which of those criteria are most appropriate for suspecting and then establishing an ME/CFS diagnosis for clinical practice.

1.1.1. Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Objective	To identify and describe published peer-reviewed diagnostic criteria for ME/CFS, which are based on consensus/guidelines.
Population and setting	Adults, children and young people who are suspected of having ME/CFS.
Review strategy	Synthesis of evidence. Results presented in table format. Assessment of the quality of the evidence is based on AGREE II.[10]

1.1.2. 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 describes the methods for the quality appraisal of the identified diagnostic criteria.

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

1.1.3. Effectiveness evidence

1.1.3.1. Included studies

Nine studies (10 publications) were included.[15-17, 42, 55, 59, 66, 124, 140, 147]

1.1.3.2. Excluded studies

See the excluded studies list in Appendix H

1.1.4. Summary of studies included in the effectiveness evidence

Table 2 summarises the criteria developed for both children and adults and Table 3 summarises criteria specifically designed for children. These include a description of their methodology and a summary of the quality appraisal (see Appendix D for an explanation of the quality criteria and Appendix E for the full quality appraisal for each study).

Table 4 provides a more concise 'side-by-side' summary of the criteria. Four of the criteria were developed for use in a clinical context[15, 59, 124, 140], three were developed for research purposes[42, 55, 147] and two were developed for use in both settings.[17, 66]

1 **Table 2: Summary of evidence for criteria aimed at both adults and children.**

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see Appendix D and E)
Fukuda 1994[42]	FUKUDA CRITERIA (RESEARCH) Clinically evaluate cases of prolonged or chronic fatigue by: 1. History and physical examination [A through history that covers medical and psycho-social circumstances at the onset of fatigue; depression or other psychiatric disorders; episodes of medically unexplained symptoms; alcohol or other substance abuse; and current use of prescription and over-the-counter medications and food supplements] 2. Mental status examination (abnormalities require appropriate psychiatric, psychologic, or neurologic examination) [A mental status examination to identify abnormalities in mood, intellectual function, memory, and personality. Particular attention should be directed toward current symptoms of depression or anxiety, self-destructive thoughts, and observable signs such as psychomotor retardation. Evidence of a psychiatric or neurologic disorder requires that an appropriate psychiatric, psychological, or neurologic evaluation be done] 3. Tests (abnormal results that strongly suggest an exclusionary condition must be resolved). Screening lab tests, including complete blood count with leukocyte differential; erythrocyte sedimentation rate; serum levels of alanine aminotransferase, total protein, albumin, globulin, alkaline phosphatase, calcium, phosphorus, glucose, blood urea nitrogen, electrolytes, and creatinine; determination of thyroid-stimulating hormone; and urinalysis. Plus additional tests as clinically indicated to exclude other diagnoses. [The use of tests to diagnose the chronic fatigue syndrome (rather than to exclude other diagnostic possibilities) should be done only in the setting of protocol-based research. The fact that such tests are investigational and do not aid in diagnosis or management should be explained to the patient].	No methodology described in detail. Guidelines developed by the International Chronic Fatigue Syndrome Study Group. Some detail in terms of the rationale of the criteria – as a revision of the 1988 CFS working case definition. The purpose of this revision was to address criticisms of the 1988 definition. Physical signs were dropped from the 1988 inclusion criteria because the group agreed that their presence had not been reliably documented in the literature. The required number of symptoms was dropped from 8 to 4 and the list of symptoms reduced from 11 to 8 because it was agreed that the 1988 system was too restrictive without increasing homogeneity. Disagreement during the development of these criteria was described, between those members favouring a more restrictive approach and those members favouring a broader approach, but it is unclear how this was resolved. The paper also describes difficulties around the definition of fatigue. The definition held by this group was that of 'severe mental and physical exhaustion, which differs from somnolence or lack of motivation and	Scope and purpose: met Stakeholder involvement: partial Rigour of development: not met Clarity of presentation: met Applicability: not met Editorial independence: not met **Overall rating: Very serious limitations**

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see Appendix D and E)
	EXCLUDE CASE IF ANOTHER CAUSE FOR CHRONIC FATIGUE IS FOUND The following conditions exclude a patient from the diagnosis of unexplained chronic fatigue. 1. Any active medical condition that may explain the presence of chronic fatigue, such as untreated hypothyroidism, sleep apnoea, and narcolepsy, and iatrogenic conditions such as side effects of medication. 2. Any previously diagnosed medical condition whose resolution has not been documented beyond reasonable clinical doubt and whose continued activity may explain the chronic fatiguing illness. Such conditions may include previously treated malignancies and unresolved cases of hepatitis B or C virus infection. 3. Any past or current diagnosis of a major depressive disorder with psychotic or melancholic features; bipolar affective disorders; schizophrenia of any subtype; delusional disorders of any subtype; dementias of any subtype; anorexia nervosa; or bulimia nervosa. 4. Alcohol or other substance abuse within 2 years before the onset of the chronic fatigue and at any time afterward. 5. Severe obesity as defined by a body mass index equal to or greater than 45. Note that the following conditions do not exclude a patient from the diagnosis of unexplained chronic fatigue. 1. Any condition defined primarily by symptoms that cannot be confirmed by diagnostic laboratory tests, including fibromyalgia, anxiety disorders, somatoform disorders, nonpsychotic or non-	which is not attributable to exercise or diagnostic disease'.	

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see Appendix D and E)
	melancholic depression, neurasthenia, and multiple chemical sensitivity disorder. 2. Any condition under specific treatment sufficient to alleviate all symptoms related to that condition and for which the adequacy of treatment has been documented. Such conditions include hypothyroidism for which the adequacy of replacement hormone has been verified by normal thyroid-stimulating hormone levels or asthma in which the adequacy of treatment has been determined by pulmonary function and other testing. 3. Any condition, such as Lyme disease or syphilis, that was treated with definitive therapy before development of chronic symptomatic sequelae. 4. Any isolated and unexplained physical examination finding or laboratory or imaging test abnormality that is insufficient to strongly suggest the existence of an exclusionary condition. Such conditions include an elevated antinuclear antibody titer that is inadequate to strongly support a diagnosis of a discrete connective tissue disorder without other laboratory or clinical evidence. OR IF NO EXCLUSION CRITERIA **Classify case as either chronic fatigue syndrome or idiopathic chronic fatigue if fatigue persists or relapses for >6 months** **Classify as chronic fatigue syndrome if**: 1. Criteria for severity of fatigue are met [clinically evaluated, un-explained, persistent or relapsing chronic fatigue that is of new or definite onset (has not been lifelong); is not the result of ongoing exertion; is not substantially alleviated by rest; and results in		

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see Appendix D and E)
	substantial reduction in previous levels of occupational, educational, social, or personal activities], and 2. Four or more of the following symptoms are concurrently present for >6 months: • Impaired memory or concentration • Sore throat • Tender cervical or axillary lymph nodes • Muscle pain • Multi-joint pain • New headaches • Unrefreshing sleep • Post-exertion malaise **Classify as idiopathic chronic fatigue** if fatigue severity or symptom criteria for chronic fatigue syndrome are not met.		
Carruthers 2011[16, 17]	MYALGIC ENCEPHALOMYELITIS: INTERNATIONAL CONSENSUS CRITERIA - ADULT AND PAEDIATRIC (CLINICAL AND RESEARCH) Although signs and symptoms of ME/CFS are dynamically interactive and causally connected, the criteria are grouped by regions of pathophysiology to provide general focus. A patient will need to meet the criteria for the following: • post-exertional neuroimmune exhaustion (A), • at least one symptom from three neurological impairment categories (B),	An International Consensus Panel comprising clinicians, researchers, university teachers and a lay-member from 13 nations and from a range of medical areas developed the guideline. This was a very experienced group, with good academic credentials. In the criteria primer, the credentials were reported as follows:	Scope and purpose: met Stakeholder involvement: partial Rigour of development partial

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see Appendix D and E)
	• at least one symptom from three immune/gastro-intestinal/ genitourinary impairment categories (C),and • at least one symptom from energy metabolism/transport impairments(D). A. **Post-exertional neuro-immune exhaustion (PENE pen'-e): Compulsory** This cardinal feature is a pathological inability to produce sufficient energy on demand with prominent symptoms primarily in the neuro-immune regions. Characteristics are as follows: 1. Marked, rapid physical and/or cognitive fatigability in response to exertion, which may be minimal such as activities of daily living or simple mental tasks, can be debilitating and cause a relapse. 2. Post exertional symptom exacerbation: e.g. acute flu-like symptoms, pain and worsening of other symptoms. 3. Post-exertional exhaustion may occur immediately after activity or be delayed by hours or days. 4. Recovery period is prolonged, usually taking 24h or longer. A relapse can last days, weeks or longer. 5. Low threshold of physical and mental fatigability (lack of stamina) results in a substantial reduction in pre-illness activity level. *Operational notes: For a diagnosis of ME, symptom severity must result in a significant reduction of a patient's premorbid activity level. Mild (an approximate 50% reduction in pre-illness activity level), moderate (mostly housebound), severe (mostly bedridden) or very severe (totally bedridden and need help with basic functions). There may be marked fluctuation of symptom severity and hierarchy from day to day or hour to hour. Consider activity, context and interactive effects. Recovery time: e.g.*	• diagnosed and/or treated more than 50 000 patients who have ME; • more than 500 years of clinical experience; • approximately 500 years of teaching experience; • authored hundreds of peer-reviewed publications, as well as written chapters and medical books; and • several members have co-authored previous criteria. The rationale for the development of the ICC was to utilize current research knowledge to identify objective, measurable and reproducible abnormalities that directly reflect the interactive, regulatory components of the underlying pathophysiology of ME. Specifically, the ICC select patients who exhibit explicit multi-systemic neuropathology, and have a pathological low threshold of physical and mental fatigability in response to exertion. Cardiopulmonary exercise test-retest studies have confirmed many post-exertional abnormalities. Criterial symptoms are compulsory and identify patients who have greater physical, cognitive and functional impairments.	Clarity of presentation: met Applicability: partial Editorial independence: partial **Overall rating: very serious limitations**

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see Appendix D and E)
	Regardless of a patient's recovery time from reading for ½ hour, it will take much longer to recover from grocery shopping for ½ hour and even longer if repeated the next day – if able. Those who rest before an activity or have adjusted their activity level to their limited energy may have shorter recovery periods than those who do not pace their activities adequately. Impact: e.g. An outstanding athlete could have a 50% reduction in his/her pre-illness activity level and is still more active than a sedentary person. B. **Neurological impairments** At least one symptom from three of the following four symptom categories 1. Neurocognitive impairments a. Difficulty processing information: slowed thought, impaired concentration e.g. confusion, disorientation, cognitive overload, difficulty with making decisions, slowed speech, acquired or exertional dyslexia b. Short-term memory loss: e.g. difficulty remembering what one wanted to say, what one was saying, retrieving words, recalling information, poor working memory 2.Pain a. Headaches: e.g. chronic, generalized headaches often involve aching of the eyes, behind the eyes or back of the head that may be associated with cervical muscle tension; migraine; tension headaches b. Significant pain can be experienced in muscles, muscle-tendon junctions, joints, abdomen or chest. It is non inflammatory in nature and often migrates. e.g.	The ICC advance the successful strategy of the Canadian Consensus Criteria (CCC) of grouping coordinated patterns of symptom clusters that identify areas of pathology. There were no industry related conflicts. The group's expertise and experience, as well as the literature, were utilized in an iterative succession of revisions. The group achieved 100% consensus through a Delphi-style approach. However details are not provided.	

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see Appendix D and E)
	generalized hyperalgesia, widespread pain (may meet fibromyalgia criteria), myofascial or radiating pain 3. Sleep disturbance a. Disturbed sleep patterns: e.g. insomnia, prolonged sleep including naps, sleeping most of the day and being awake most of the night, frequent awakenings, awaking much earlier than before illness onset, vivid dreams/ nightmares b. Unrefreshed sleep: e.g. awaken feeling exhausted regardless of duration of sleep, day-time sleepiness 4. Neurosensory, perceptual and motor disturbances a. Neurosensory and perceptual: e.g. inability to focus vision, sensitivity to light, noise, vibration, odour, taste and touch; impaired depth perception b. Motor: e.g. muscle weakness, twitching, poor coordination, feeling unsteady on feet, ataxia *Notes: Neurocognitive impairments, reported or observed, become more pronounced with fatigue. Overload phenomena may be evident when two tasks are performed simultaneously. Abnormal accommodation responses of the pupils are common. Sleep disturbances are typically expressed by prolonged sleep, sometimes extreme, in the acute phase and often evolve into marked sleep reversal in the chronic stage. Motor disturbances may not be evident in mild or moderate cases but abnormal tandem gait and positive Romberg test may be observed in severe cases.* C. **Immune, gastro-intestinal and genitourinary Impairments** At least one symptom from three of the following five symptom categories:		

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see Appendix D and E)
	1. Flu-like symptoms may be recurrent or chronic and typically activate or worsen with exertion. e.g. sore throat, sinusitis, cervical and/or axillary lymph nodes may enlarge or be tender on palpitation 2. Susceptibility to viral infections with prolonged recovery periods 3. Gastro-intestinal tract: e.g. nausea, abdominal pain, bloating, irritable bowel syndrome 4. Genitourinary: e.g. urinary urgency or frequency, nocturia 5. Sensitivities to food, medications, odours or chemicals *Notes: Sore throat, tender lymph nodes, and flu-like symptoms obviously are not specific to ME but their activation in reaction to exertion is abnormal. The throat may feel sore, dry and scratchy. Faucial injection and crimson crescents may be seen in the tonsillar fossae, which are an indication of immune activation.* D. **Energy production/transportation impairments: At least one symptom** 1. Cardiovascular: e.g. inability to tolerate an upright position - orthostatic intolerance, neutrally mediated hypotension, postural orthostatic tachycardia syndrome, palpitations with or without cardiac arrhythmias, light-headedness/dizziness 2. Respiratory: e.g. air hunger, laboured breathing, fatigue of chest wall muscles 3. Loss of thermostatic stability: e.g. subnormal body temperature, marked diurnal fluctuations; sweating episodes, recurrent feelings of feverishness with or without low grade fever, cold extremities 4. Intolerance of extremes of temperature		

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see Appendix D and E)
	Notes: Orthostatic intolerance may be delayed by several minutes. Patients who have orthostatic intolerance may exhibit mottling of extremities, extreme pallor or Raynaud's Phenomenon. In the chronic phase, moons of finger nails may recede. **Paediatric considerations** Symptoms may progress more slowly in children than in teenagers or adults. In addition to post-exertional neuroimmune exhaustion, the most prominent symptoms tend to be neurological: headaches, cognitive impairments, and sleep disturbances. 1. Headaches: Severe or chronic headaches are often debilitating. Migraine may be accompanied by a rapid drop in temperature, shaking, vomiting, diarrhoea and severe weakness. 2. Neurocognitive impairments: Difficulty focusing eyes and reading are common. Children may become dyslexic, which may only be evident when fatigued. Slow processing of information makes it difficult to follow auditory instructions or take notes. All cognitive impairments worsen with physical or mental exertion. Young people will not be able to maintain a full school programme. 3. Pain may seem erratic and migrate quickly. Joint hypermobility is common. *Notes: Fluctuation and severity hierarchy of numerous prominent symptoms tend to vary more rapidly and dramatically than in adults.* **Classification** —Myalgic encephalomyelitis —Atypical myalgic encephalomyelitis: meets criteria for post exertional neuroimmune exhaustion but has a limit of two less than required of the		

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see Appendix D and E)
	remaining criterial symptoms. Pain or sleep disturbance may be absent in rare cases. **Exclusions**: As in all diagnoses, exclusion of alternate explanatory diagnoses is achieved by the patient's history, physical examination, and laboratory/ biomarker testing as indicated. It is possible to have more than one disease but it is important that each one is identified and treated. Primary psychiatric disorders, somatoform disorder and substance abuse are excluded. Paediatric: 'primary' school phobia. **Comorbid entities**: Fibromyalgia, myofascial pain syndrome, temporomandibular joint syndrome, irritable bowel syndrome, interstitial cystitis, Raynaud's phenomenon, prolapsed mitral valve, migraines, allergies, multiple chemical sensitivities, Hashimoto's thyroiditis, Sicca syndrome, reactive depression. Migraine and irritable bowel syndrome may precede ME but then become associated with it. Fibromyalgia overlaps.		
Carruthers 2003[15]	<u>ME/CFS: CLINICAL WORKING CASE DEFINITION (CLINICAL)</u> A patient with ME/CFS will meet the criteria for fatigue, post-exertional malaise and/or fatigue, sleep dysfunction, and pain; have two or more neurological/cognitive manifestations and one or more symptoms from two of the categories of autonomic, neuroendocrine and immune manifestations; and adhere to item 7. 1. Fatigue: The patient must have a significant degree of new onset, unexplained, persistent, or recurrent physical and mental fatigue that substantially reduces activity level. 2. Post-Exertional Malaise and/or Fatigue: There is an inappropriate loss of physical and mental stamina, rapid	An Expert Subcommittee of Health Canada selected an expert guideline panel comprising physicians, University teachers and researchers. A Consensus Workshop was held to complete the review process and form consensus for the diagnostic criteria. However few details of methodology are given. .	Scope and purpose: met Stakeholder involvement: partial Rigour of development: not met Clarity of presentation: met

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see Appendix D and E)
	muscular and cognitive fatigability, post exertional malaise and/or fatigue and/or pain and a tendency for other associated symptoms within the patient's cluster of symptoms to worsen. There is a pathologically slow recovery period - usually 24 hours or longer. 3. Sleep Dysfunction:* There is unrefreshed sleep or sleep quantity or rhythm disturbances such as reversed or chaotic diurnal sleep rhythms. 4. Pain:* There is a significant degree of myalgia. Pain can be experienced in the muscles and/or joints, and is often widespread and migratory in nature. Often there are significant headaches of new type, pattern or severity. 5. Neurological/Cognitive Manifestations: Two or more of the following difficulties should be present: confusion, impairment of concentration and short-term memory consolidation, disorientation, difficulty with information processing, categorizing and word retrieval, and perceptual and sensory disturbances – e.g., spatial instability and disorientation and inability to focus vision. Ataxia, muscle weakness and fasciculations are common. There may be overload phenomena: cognitive, sensory – e.g., photophobia and hypersensitivity to noise–and/or emotional overload, which may lead to “crash” periods and/or anxiety. 6. At Least One Symptom from Two of the Following Categories: a. Autonomic Manifestations: orthostatic intolerance – neurally mediated hypotension (NMH), postural orthostatic tachycardia syndrome (POTS), delayed		Applicability: not met Editorial independence: not met **Overall rating: very serious limitations**

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see Appendix D and E)
	postural hypotension; light-headedness; extreme pallor; nausea and irritable bowel syndrome; urinary frequency and bladder dysfunction; palpitations with or without cardiac arrhythmias; exertional dyspnoea. b. Neuroendocrine Manifestations: loss of thermostatic stability – subnormal body temperature and marked diurnal fluctuation, sweating episodes, recurrent feelings of feverishness and cold extremities; intolerance of extremes of heat and cold; marked weight change– anorexia or abnormal appetite; loss of adaptability and worsening of symptoms with stress. c. Immune Manifestations: tender lymph nodes, recurrent sore throat, recurrent flu-like symptoms, general malaise, new sensitivities to food, medications and/or chemicals. 7. The illness persists for at least six months. It usually has a distinct onset,** although it may be gradual. Preliminary diagnosis may be possible earlier. Three months is appropriate for children. To be included, the symptoms must have begun or have been significantly altered after the onset of this illness. It is unlikely that a patient will suffer from all symptoms in criteria 5 and 6. The disturbances tend to form symptom clusters that may fluctuate and change over time. Children often have numerous prominent symptoms but their order of severity tends to vary from day to day.		

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see Appendix D and E)
	*There is a small number of patients who have no pain or sleep dysfunction, but no other diagnosis fits except ME/CFS. A diagnosis of ME/CFS can be entertained when this group has an infectious illness type onset. **Some patients have been unhealthy for other reasons prior to the onset of ME/CFS and lack detectable triggers at onset and/or have more gradual or insidious onset. **Exclusions**: Exclude active disease processes that explain most of the major symptoms of fatigue, sleep disturbance, pain, and cognitive dysfunction. It is essential to exclude certain diseases, which would be tragic to miss: Addison's disease, Cushing's Syndrome, hypothyroidism, hyperthyroidism, iron deficiency, other treatable forms of anaemia, iron overload syndrome, diabetes mellitus, and cancer. It is also essential to exclude treatable sleep disorders such as upper airway resistance syndrome and obstructive or central sleep apnoea; rheumatological disorders such as rheumatoid arthritis, lupus, polymyositis and polymyalgia rheumatica; immune disorders such as AIDS; neurological disorders such as multiple sclerosis (MS), Parkinsonism, myasthenia gravis and B12 deficiency; infectious diseases such as tuberculosis, chronic hepatitis, Lyme disease, etc.; primary psychiatric disorders and substance abuse. Exclusion of other diagnoses, which cannot be reasonably excluded by the patient's history and physical examination, is achieved by laboratory testing and imaging. If a potentially confounding medical condition is under control, then the diagnosis of ME/CFS can be entertained if patients meet the criteria otherwise. **Co-Morbid Entities**: Fibromyalgia Syndrome (FMS), Myofascial Pain Syndrome (MPS), Temporomandibular Joint Syndrome (TMJ), Irritable Bowel Syndrome (IBS), Interstitial Cystitis, Irritable Bladder Syndrome, Raynaud's Phenomenon, Prolapsed Mitral Valve, Depression, Migraine,		

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see Appendix D and E)
	Allergies, Multiple Chemical Sensitivities (MCS), Hashimoto's thyroiditis, Sicca Syndrome, etc. Such co-morbid entities may occur in the setting of ME/CFS. Others such as IBS may precede the development of ME/CFS by many years, but then become associated with it. The same holds true for migraines and depression. Their association is thus looser than between the symptoms within the syndrome. ME/CFS and FMS often closely connect and should be considered to be "overlap syndromes." **Idiopathic Chronic Fatigue**: If the patient has unexplained prolonged fatigue (6 months or more) but has insufficient symptoms to meet the criteria for ME/CFS, it should be classified as idiopathic chronic fatigue. **Special considerations for children**: Hierarchy of symptom severity may vary from day to day. Severe and generalised pain is common. Dyslexia, tearfulness, physical weakness, exhaustion and profound mood changes occur. Physically activity may be avoided and schoolwork declines, particularly in numerate and scientific studies. School phobia is often observed. **Notes on ME and CFS** The guideline group regarded ME and CFS as the same disorder.		
Sharpe, 1991[147]	OXFORD CRITERIA (RESEARCH) **Signs** There are no clinical signs that are characteristic of the condition, but patients should be fully examined, and the presence or absence of signs reported. **Syndromes**	The aim of the meeting was to seek agreement amongst research workers on recommendations for the conduct and reporting of future studies of patients with chronic fatigue. The meeting was restricted to invited research workers, who had all studied patients with CFS. The disciplines represented included biochemistry, general medicine, general practice,	Scope and purpose: met Stakeholder involvement: partial Rigour of development: not met

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see Appendix D and E)
	Two broad syndromes can be defined: **Chronic fatigue syndrome (CFS)** (a) A syndrome characterized by fatigue as the principal symptom. (b) A syndrome of definite onset that is not life-long. (c) The fatigue is severe, disabling, and affects physical and mental functioning. (d) The symptom of fatigue should have been present for a minimum of 6 months during which it was present for more than 50% of the time. (e) Other symptoms may be present, particularly myalgia, mood and sleep disturbance. (f) Certain patients should be excluded from the definition. They include: (i) Patients with established medical conditions known to produce chronic fatigue (eg severe anaemia). Such patients should be excluded whether the medical condition is diagnosed at presentation or only subsequently. All patients should have a history and physical examination performed by a competent physician. (ii) Patients with a current diagnosis of schizophrenia, manic depressive illness, substance abuse, eating disorder or proven organic brain disease. Other psychiatric disorders (including depressive illness, anxiety disorders, and hyperventilation syndrome) are not necessarily reasons for exclusion. **Post-infectious fatigue syndrome (PIFS)** This is a subtype of CFS which either follows an infection or is associated with a current infection (although whether such associated infection is of aetiological significance is a topic for research). To meet research criteria for PIFS patients must (i) fulfil criteria for CFS as defined above, and (ii) should also fulfil the following additional criteria:	imaging, immunology, infectious diseases, microbiology, neurology, physiology, psychiatry, and psychology. Before the meeting all participants (and several others who were unable to attend) were circulated with a questionnaire, and their responses used to draw up an initial discussion document which formed the basis of discussion during the meeting. Points on which agreement was reached were recorded and a draft of this paper circulated to participants.	Clarity of presentation: partial Applicability: not met Editorial independence: not met **Overall rating: very serious limitations**

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see Appendix D and E)
	(a) There is definite evidence of infection at onset or presentation (a patient's self-report is unlikely to be sufficiently reliable). (b) The syndrome is present for a minimum of 6 months after onset of infection. (c) The infection has been corroborated by laboratory evidence. **Glossary** This glossary provides provisional definitions of the principal symptoms and suggests how they may be described. Each symptom is considered as follows: (i) A description of the symptom (what it is). (ii) What it is to be distinguished from (what it is not). (iii) Criteria for rating its presence. (iv) Additional description. **Fatigue** (i) When used to describe a symptom this is a subjective sensation and has a number of synonyms including, tiredness and weariness. A clear description of the relationship of fatigue to activity is preferred to the term fatigability. Two aspects of fatigue are commonly reported: mental and physical. Mental fatigue is a subjective sensation characterized by lack of motivation and of alertness. Physical fatigue is felt as lack of energy or strength and is often felt in the muscles. (ii) Fatigue as a symptom should be distinguished from low mood and from lack of interest. The symptom of fatigue should not be confused with impairment of performance as measured by physiological or psychological testing. The physiological definition of fatigue is of a failure to sustain muscle force or power output. (iii) To be regarded as a symptom, fatigue must: (a) be complained of;		

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see Appendix D and E)
	(b) significantly affect the person's functioning; (c) should be disproportionate to exertion; (d) should represent a clear change from a previous state; and (e) be persistent, or if intermittent should be present more than 50% of the time. (iv) The symptom should be described as follows: (a) severity: mild, moderate, or severe; (b) frequency: continuous or intermittent. If intermittent the proportion of the time present; (c) relation to activity: it should be stated whether the fatigue is greatly increased by minor exertion and whether it occurs at rest. **Disability** (i) This refers to any restriction or lack (resulting from loss of psychological or physiological function) of ability to perform an activity in the manner or within the range considered normal for a human being (i.e. things people cannot do in the areas of occupational, social, and leisure activities because of their illness). (ii) Disability (e.g. inability to walk) should be distinguished from impairment of function (e.g. weak legs), and from handicap (e.g. unable to work). (iii) There should be a definite and persistent change from a previous level of functioning and it is desirable to seek supportive evidence from an informant. (iv) The disability should be described as follows: (a) area of disability (i.e. occupational, social, leisure, self-care); (b) degree of disability. **Mood disturbance**		

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see Appendix D and E)
	(i) The term mood disturbance has been used to include depression, loss of interest and loss of pleasure (anhedonia), anxiety, emotional lability and irritability. (ii) These phenomena should be distinguished from each other. (iii) To be regarded as a symptom the mood disturbance should be (a) complained of; (b) should represent a significant change from a previous state; and (c) should be relatively persistent or recurrent. Judgements of the appropriateness of mood disturbance are unreliable and should be avoided. (iv) The symptom should be described as follows: (a) type: depressed mood, anhedonia, anxious mood, emotional lability, irritability; (b) severity: standard scales are available to assess the severity of depressed mood and anxiety. In addition it should be determined whether the patient's disorder is sufficient to meet operational diagnostic criteria for major depressive disorder, generalized anxiety disorder or panic disorder according to a recognized psychiatric classification, eg the current edition ofthe Diagnostic and Statistical Manual of the American Psychiatric Association, DSM-III-R'7. (c) duration and frequency of the mood disturbance should be reported. **Myalgia** (i) This refers to the symptom of pain or aching, felt in the muscles. (ii) It should be distinguished from feelings of weakness and from pain felt in other areas such as joints. (iii) The myalgia should be (a) complained of;		

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see Appendix D and E)
	(b) be disproportionate to exertion; (c) be a change from a previous state; (d) should be persistent or recurrent. (iv) The symptom should be described as follows: (a) severity: mild, moderate, or severe; (b) frequency and duration; (c) relation to exertion: if after exertion the time of onset relative to the exertion, and duration should be described. **Sleep disturbance** (i) The symptom of sleep disturbance refers to a subjective report of a change in the duration or quality of sleep. (ii) Sleep disturbance should be distinguished from feelings of daytime fatigue or tiredness. (iii) The sleep disturbance should (a) be complained of; (b) not simply be a response to external disturbance; (c) be a change from the previous state; (d). be persistent. (iv) The symptom should be described as follows: (a) type: hypersomnia or increased sleep; insomnia or reduced sleep (which should be further described as either difficulty getting off to sleep, early waking, or subjectively disturbed or unrefreshing sleep); (b) severity: the amount of change induration of sleep should be quantified in hours.		
Institute of Medicine 2015[59]	IOM DIAGNOSTIC CRITERIA FOR ME/CFS (Systemic Exertional Intolerance Disease [SEID]) (CLINICAL)	The Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue	Scope and purpose: met

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see Appendix D and E)
	Diagnosis requires that the patient have the following three symptoms: 1. A substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest, 2. Post-exertional malaise,* and 3. Unrefreshing sleep* At least one of the two following manifestations is also required: 1. Cognitive impairment* or 2. Orthostatic intolerance * Frequency and severity of symptoms should be assessed. The diagnosis of ME/CFS should be questioned if patients do not have these symptoms at least half of the time with moderate, substantial, or severe intensity. **Special notes on paediatric ME/CFS** Although a common set of criteria are proposed for both adults and children, the IOM made the following statement relating to children. There is sufficient evidence that orthostatic intolerance and autonomic dysfunction are common in paediatric ME/CFS; that neurocognitive abnormalities emerge when paediatric ME/CFS patients are tested under conditions of orthostatic stress or distraction; and that there is a high prevalence of profound fatigue, unrefreshing sleep, and post-exertional exacerbation of symptoms in these patients. There also is sufficient	Syndrome comprised 15 members with expertise in clinical care for ME/CFS, paediatrics, infectious disease, epidemiology, immunology, rheumatology, behavioural health, pain, sleep, primary care, genetics, exercise physiology, neurology/neuropathology, clinical case definitions, and consensus processes. In addition to their scientific expertise, two committee members are or have been patients, and one is a family member/caregiver of a patient with ME/CFS. The committee engaged in a number of activities to inform its work: • The committee heard testimony, primarily from patients and advocates, on two occasions. The agendas for these sessions are provided in Appendix A. • The committee carefully considered hundreds of public comments submitted through its public portal for this study.2 • The committee heard testimony from selected experts in this field • The committee conducted a comprehensive literature review. The review included a search of eight databases for all articles published since 1950 related to ME, CFS, ME/CFS, and other terms used to describe this disorder. Additional	Stakeholder involvement: met Rigour of development: partial Clarity of presentation: met Applicability: partial Editorial independence: partial **Overall rating: serious limitations**

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see Appendix D and E)
	evidence that paediatric ME/CFS can follow acute infectious mononucleosis and EBV.	citations and grey literature (i.e., non-commercially published) were identified by the IOM staff, committee members, and the public and from references in pertinent articles. After a preliminary review of the literature, the committee directed the IOM staff to divide the articles into topics most central to its work: eight symptoms or symptom categories (for children/ adolescents and adults) and three additional topics. For some of these topics, the committee reviewed abstracts of all of the relevant literature. For other topics, the committee developed specific questions with inclusion/exclusion criteria, which the IOM staff used to exclude irrelevant abstracts. In all cases, research groups of two to five committee members assigned to each topic reviewed the abstracts to determine which articles were pertinent to the committee's charge. These groups then read the full text of these articles, extracting their findings and using an adapted "GRADE grid" to record judgments as to whether there was sufficient evidence that certain symptoms and abnormalities define either ME/CFS or a particular subtype of the disorder • The committee received and considered preliminary findings from CDC's ongoing Multi-Site Clinical	

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see Appendix D and E)
		Assessment of CFS. The committee was unable however, to obtain input from NIH's Evidence-based Methodology Workshop for ME/CFS until after this study was concluded. • The committee consulted with a health communications specialist and a statistician to obtain additional expertise in addressing the statement of task. In deliberating on its recommendations, the committee carefully considered the above sources of information. The collated judgments were used to facilitate discussion. Final recommendations regarding diagnostic criteria were made by consensus after deliberation by the committee as a whole.	
National Collaborating Centre for Primary Care, 2007[124]	<u>NICE CRITERIA (CLINICAL)</u> 1.2.1.1 'CFS/ME' is recognised on clinical grounds alone. Primary healthcare professionals should be familiar with and be able to identify the characteristic features of 'CFS/ME'. 1.2.1.2 Healthcare professionals should **consider the possibility** of 'CFS/ME' if a person has: • fatigue with all of the following features: - new or had a specific onset (that is, it is not lifelong) - persistent and/or recurrent - unexplained by other conditions	The Guideline Development Group (GDG) was deliberately convened to have a sufficiently large and broad membership to reflect the wider expertise amongst the various specialties to which people with 'CFS/ME' may be referred. It chiefly comprised patient representatives and healthcare professionals with daily, clinical experience of treating 'CFS/ME', rather than purely academic expertise. Nominations for GDG members were invited from various stakeholder organisations and members were selected to ensure appropriate	Scope and purpose: met Stakeholder involvement: met Rigour of development: partial Clarity of presentation: met

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see Appendix D and E)
	- has resulted in a substantial reduction in activity level characterised by post-exertional malaise and/or fatigue (typically delayed, for example by at least 24 hours, with slow recovery over several days) and • one or more of the following symptoms: - difficulty with sleeping, such as insomnia, hypersomnia, unrefreshing sleep, a disturbed sleep–wake cycle - muscle and/or joint pain that is multi-site and without evidence of inflammation - headaches - painful lymph nodes without pathological enlargement - sore throat - cognitive dysfunction, such as difficulty thinking, inability to concentrate, impairment of short-term memory, and difficulties with word-finding, planning/organising thoughts and information processing; physical or mental exertion makes symptoms worse - general malaise or 'flu-like' symptoms - dizziness and/or nausea - palpitations in the absence of identified cardiac pathology. 1.3.1.1 A diagnosis should be made after other possible diagnoses have been excluded and the symptoms have persisted for: • 4 months in an adult • 3 months in a child or young person; the diagnosis should be made or confirmed by a paediatrician. 1.3.1.3 The diagnosis of CFS/ME should be reconsidered if none of the following key features are present: • post-exertional fatigue or malaise • cognitive difficulties • sleep disturbance	representation. Consensus development methods were used in addition to the usual guideline development processes. A comprehensive literature review was used to inform group decisions. An external consultation process was used.	Applicability: partial Editorial independence: not met **Overall rating: serious limitations**

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see Appendix D and E)
	• chronic pain		
Holmes 1988[55]	<u>CHRONIC FATIGUE SYNDROME: A WORKING CASE DEFINITION (RESEARCH)</u> A case of Chronic Fatigue Syndrome must fulfil major criteria 1 and 2, and the following minor criteria: 6 or more of the 11 symptom criteria and 2 or more of the 3 physical criteria; or 8 or more of the 3 physical criteria; or 8 or more of the 11 symptom criteria. **Major criteria** 1.New onset of persistent or relapsing, debilitating fatigue or easy fatigability in a person who has no previous history of similar symptoms, that does not resolves with bedrest, and that is severe enough to reduce or impair average daily activity below 50% of the patient's premorbid activity level for a period of at least 6 months. 2. Other clinical conditions that may produce similar symptoms must be excluded by thorough evaluation, based on history, physical examination, and appropriate laboratory findings. These conditions include malignancy; auto-immune disease; localised infection (such as occult abscess); chronic or subacute bacterial disease (such as endocarditis, Lyme disease, or tuberculosis), fungal disease (such as histoplasmosis, blastomycosis, or coccidiodomycosis) and parasitic disease (such as toxoplasmosis, amebiasis, giardiasis, or helminthic infestation); disease related to human immunodeficiency virus (HIV) infection; chronic psychiatric disease, either newly diagnosed or by history (such as exogenous depression; hysterical personality disorder; anxiety neurosis; schizophrenia; or chronic use of major tranquilisers, lithium, or anti-depressive medications); chronic inflammatory disease (such as sarcoidosis, Wegener granulomatosis, or chronic hepatitis); neuromuscular disease (such as multiple sclerosis or myasthenia gravis);	An informal working group of public health epidemiologists, academic researchers, and clinicians was organised to develop a consensus on the salient characteristics of CFS, and to devise a definition of the disorder that will form the basis of further research. However further details are not given.	Scope and purpose: met Stakeholder involvement: partial Rigour of development: not met Clarity of presentation: met Applicability: not met Editorial independence: not met **Overall rating: very serious limitations**

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see Appendix D and E)
	endocrine disease (such as hypothyroidism, Addison disease, Cushing syndrome, or diabetes mellitus); drug dependency or abuse (such as alcohol, controlled prescription drugs, or illicit drugs); side effects of a chronic medication or other toxic agent (such as a chemical solvent, pesticide, or heavy metal); or other known or defined chronic pulmonary, cardiac, gastrointestinal, hepatic, renal, or hematologic disease. Specific laboratory tests or clinical measurements are not required to satisfy the definition of the chronic fatigue syndrome, but the recommended evaluation includes serial weight measurements (weight change of >10% in the absence of dieting suggests other diagnoses); serial morning and afternoon temperature measurements; complete blood count and differential; serum electrolytes; glucose; creatinine, blood urea nitrogen; calcium, phosphorous; total bilirubin, alkaline phosphatase, serum aspartate aminotransferase, serum alanine aminotransferase; creatinephosphokinase or aldolase; urinalysis; postero-anterior and lateral chest roentgenograms; detailed personal and family psychiatric history; erythrocyte sedimentation rate; antinuclear antibody; thyroid-stimulating hormone level; HIV antibody measurement; and intermediate-strength purified protein derivative (PPD) skin test with controls. If any of the results from these tests are abnormal, the physician should search for other conditions that may cause such a result. If no such conditions are detected by a reasonable evaluation, this criterion is satisfied. **Minor criteria** *Symptom criteria* To fulfil a symptoms criterion, a symptom must have begun at or after the time of onset of increased fatigability, and must have persisted or recurred over a period of at least 6 months (individual symptoms may or may not have occurred simultaneously). Symptoms include:		

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see Appendix D and E)
	1. Mild fever – oral temperature between 37.5 Celsius and 38.6 Celsius, if measured by the patient – or chills. (Note: oral temperatures of greater than 38.6 Celsius are less compatible with chronic fatigue syndrome and should prompt studies for other causes of illness.) 2. Sore throat. 3. Painful lymph nodes in the anterior or posterior cervical or axillary distribution. 4. Unexplained generalised muscle weakness. 5. Muscle discomfort or myalgia. 6. Prolonged (24 hours of greater) generalised fatigue after levels of exercise that would have been easily tolerated in the patient's premorbid state. 7. Generalised headaches (of a type, severity, or pattern that is different from headaches the patient may have had in the premorbid state). 8. Migratory arthralgia without joint swelling or redness. 9. Neuropsychological complaints (one or more of the following: photophobia, transient visual scotomata, forgetfulness, excessive irritability, confusion, difficulty thinking, inability to concentrate, depression). 10. Sleep disturbance (hypersomnia or insomnia). 11. Description of the main symptom complex as initially developing over a few hours to a few days (this is not a true symptom, but may be considered as equivalent to the above symptoms in meeting the requirements of the case definition). *Physical criteria* Physical criteria must be documented by a physician on at least two occasions, at least 1 month apart.		

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see Appendix D and E)
	1. Low-grade fever – oral temperature between 37.6 Celsius and 38.6 Celsius, or rectal temperature between 37.8 Celsius and 38.8 Celsius (see note under Symptom Criterion 1.) 2. Non-exudative pharyngitis. 3. Palpable or tender anterior or posterior cervical or axillary lymph nodes. (Note: lymph nodes greater than 2 cm in diameter suggest other causes. Further evaluation is warranted.)		

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1 **Table 3: Summary of evidence specifically for children**

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see table 4)
Jason 2006[66]	<u>DEFINITION OF ME/CFS FOR CHILDREN (CLINICAL AND RESEARCH)</u> I. Clinically evaluated, unexplained, persistent or relapsing chronic fatigue over the past 3 months that: a. Is not the result of ongoing exertion b. Is not substantially alleviated by rest c. Results in substantial reduction in previous levels of educational, social and personal activities d. Must persist or reoccur for at least 3 months II. The concurrent occurrence of the following classic ME/CFS symptoms, which must have persisted or recurred during the past three months of illness (symptoms may predate the reported onset of fatigue). a. Post exertional malaise and/or post-exertional fatigue. With activity (it need not be strenuous and may include walking up a flight of stairs, using a computer, or reading a book), there must be a loss of physical or mental stamina, rapid/sudden muscle or cognitive fatigability, post exertional malaise and/or fatigue and a tendency for other associated symptoms within the patient's cluster of symptoms to worsen. The recovery is slow, often taking 24 hours or longer. b. Unrefreshing sleep or disturbance of sleep quantity or rhythm disturbance	Criteria developed by the International Association of Chronic Fatigue Syndrome Paediatric Case definition Working group. No description of methodology, although a literature review seems to support the set of criteria.	Scope and purpose: met Stakeholder involvement: partial Rigour of development: not met Clarity of presentation: met Applicability: not met Editorial independence: not met **Overall rating: very serious limitations**

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see table 4)
	May include prolonged sleep (including frequent naps), disturbed sleep (e.g., inability to fall asleep or early awakening), and/or day/night reversal. c. Pain (or discomfort) that is often widespread and migratory in nature. At least one symptom from any of the following: Myofascial and/or joint pain (myofascial pain can include deep pain, muscle twitches, or achy and sore muscles. Pain, stiffness or tenderness may occur in any joint but must be present in more than one joint and lacking oedema or other signs of inflammation.) Abdominal and/or head pain (May experience eye pain/sensitivity to bright light, stomach pain, nausea, vomiting, or chest pain. Headaches often described as localised behind the eyes or in the back of the head. May include headaches localised elsewhere, including migraines.) d. Two or more neurocognitive manifestations: Impaired memory (self-reported or observable disturbance in ability to recall information or events on a short-term basis) Difficulty focussing (disturbed concentration may impair ability to remain on task, to screen out extraneous/excessive stimuli in a classroom, or to focus on reading, computer/work activity, or television programs) Difficulty finding the right word Frequently forget what wanted to say Absent mindedness Slowness of thought		

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see table 4)
	Difficulty recalling information Need to focus on one thing at a time Trouble expressing thought Difficulty comprehending information Frequently lose train of thought New trouble with mathematics or other educational subjects e. At least one symptom from two of the following three categories: 1. Autonomic manifestations: neurally mediated hypotension, postural orthostatic tachycardia, delayed postural hypotension, palpitations with or without cardiac arrhythmias, dizziness, feeling unsteady on the feet – disturbed balance, shortness of breath. 2. Neuroendocrine manifestations: recurrent feelings of feverishness and cold extremities, subnormal body temperature and marked diurnal fluctuations, sweating episodes, intolerance of extremes of heat and cold, marked weight change – loss of appetite or abnormal appetite, worsening of symptoms with stress. 3. Immune manifestations: recurrent flu-like symptoms, non-exudative sore or scratchy throat, repeated fevers and sweats, lymph nodes tender to palpitation – generally minimal swelling noted new sensitivities to food, odours or chemicals. III. Exclusionary conditions: a. Any active medical condition that may explain the presence of chronic fatigue, such as i. Untreated hypothyroidism		

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see table 4)
	ii. Sleep apnoea iii. Narcolepsy iv. Malignancies v. Leukaemia vi. Unresolved hepatitis vii. Multiple sclerosis viii. Juvenile rheumatoid arthritis ix. Lupus erythematosus x. HIV/AIDS xi. Severe obesity (BMI>40) xii. Celiac disease xiii. Lyme disease b. Some active psychiatric conditions that may explain the presence of chronic fatigue, such as i. Childhood schizophrenia or psychotic disorders ii. Bipolar disorder iii. Active alcohol or substance abuse – excepts as below: 1. Alcohol or substance abuse that has been successfully treated and resolved should be considered exclusionary iv. Active anorexia nervosa or bulimia nervosa – except as below: 1. Eating disorders that have been treated and resolved should not be considered exclusionary v. Depressive disorders IV. May have presence of concomitant disorders that do not adequately explain fatigue, and are, therefore, not necessarily exclusionary.		

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see table 4)
	a. Psychiatric diagnoses such as: i. School phobia ii. Separation anxiety iii. Anxiety disorders iv. Somatoform disorders v. Depressive disorders b. Other conditions defined primarily by symptoms that cannot be confirmed by diagnostic laboratory tests, such as: i. Multiple food and/or chemical sensitivity ii. Fibromyalgia c. Any condition, that was treated with definitive therapy before development of chronic symptomatic sequelae d. Any isolated and unexplained physical examination, laboratory or imaging test abnormality that is insufficient to strongly suggest the existence of an exclusionary condition.		
Rowe 2017 [140]	<u>CRITERIA FOR THE DIAGNOSIS OF ME/CFS IN CHILDREN AND ADOLESCENTS (CLINICAL)</u> 1. Impaired function: there is loss of mental and/or physical stamina and a substantial reduction in ability to take part in personal, educational, and/or social activities 2. Post-exertional symptoms: normal activity or mild/moderate exertion is followed by worsening of malaise, fatigue, and other symptoms. Recovery takes more than 24 h 3. Fatigue: the fatigue is not the result of ongoing exertion, is not relieved by rest, and is medically unexplained. Fatigue can worsen with prolonged upright posture	Criteria developed by the International Writing Group for Paediatric ME/CFS. Developed by consensus, based on published studies and clinical expertise of experienced medical practitioners.	Scope and purpose: met Stakeholder involvement: partial Rigour of development: not met Clarity of presentation: met

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see table 4)
	4. Sleep problems: sleep is unrefreshing with disturbed quantity or rhythm that can include daytime hypersomnia, night-time insomnia, and day/night reversal 5. Cognitive problems: any of the following: difficulty in concentration or focusing, difficulty understanding information and/or expressing thoughts, difficulty finding words or numbers, impaired short-term memory, absent mindedness, slowness of thought. Cognitive problems can be provoked by, or worsen with prolonged upright posture and/or physical or mental activity. Some young patients may not recognize these problems, but they might be noticed by a parent or teacher. 6. Pain: can be widespread or localized, commonly seen are: chronic daily headaches, myalgias, abdominal pain, joint pains, sore throats, and painful lymph nodes. Pain can be worsened by prolonged upright posture. Rarely is pain absent. Other symptoms present in many, but not all, paediatric patients with ME/CFS: • Orthostatic intolerance: prolonged upright posture can induce symptoms that can include light-headedness, increased fatigue, cognitive worsening, headaches, and/or nausea. Postural tachycardia syndrome (POTS) or neurally mediated hypotension (NMH) are often present. • Hypersensitivities: to light, noise, touch, odours, and medications. • Thermo-regulatory imbalance: low body temperature, intolerance to heat and cold, and/or cold hands and feet. • Gastrointestinal symptoms: abdominal pain, nausea and/or anorexia. To diagnose ME/CFS: • Symptom criteria 1, 2, and 3 are present together with at least two of criteria 4, 5, and 6 • Symptoms are present for 6 months and some or all symptoms are present daily		Applicability: not met Editorial independence: partial **Overall rating: very serious limitations**

Study	Description of criteria	Methodology [for example, Delphi methods, consensus methods, literature searching methods, etc] used to derive the criteria	Critical appraisal of the study methods (see table 4)
	• No other diagnosis found from the history, physical examination, and medical testing • Symptom severity score: 0–4 ME/CFS unlikely; 5–12 mild/moderate ME/CFS; 13–18 moderate/severe ME/CFS Common conditions in the differential diagnosis of ME/CFS: • Adrenal insufficiency • Athletic overtraining syndrome • Bowel disorders: celiac disease, inflammatory bowel disease, and eosinophilic gastroenteritis • Chiari malformation or cervical spine stenosis • Lyme disease and other tick-borne infections • Major depression • Narcolepsy • Obstructive or central apnoea • Post-concussion syndrome • Severe anaemias • Systemic lupus erythematosis and similar autoimmune conditions • Untreated hypo- or hyper-thyroidism		

1 **Table 4: Overview of included ME/CFS criteria as categorised by the authors**

Symptom/sign category	CDC Fukuda, 1994[42]	ICC, 2011[16, 17]	Carruthers, 2003[15]	Oxford, 1991[147]	IOM, 2015[59]	NICE, 2007[124]	CDC Holmes, 1988[55]	Jason, 2006[66]	Rowe 2017[140]
	Adults and children							Children	
Post-exertional exhaustion/post-exertion malaise(PEM)/ Post-exertional symptom exacerbation (PESE) Note: the committee's preferred term is PESE	*	*	*		*	*	*	*	*
Other severe and prolonged fatigue unexplained by activity. Activity refers to any effort that uses energy and includes cognitive, physical, emotional and social activity	*	*	*	*	*	*	*	*	*
Inability to engage in pre-illness functional levels		*		*	*			*	*
Motor deficits									
Muscle weakness		*	*				*		
Other motor dysfunction (i.e. ataxia, gait disturbance, muscle twitches)		*	*					*	
Sensory deficits									
Non-vestibular sensory dysfunction (i.e. visual problems)		*	*				*		
Vestibular [or vestibular-like] symptoms (i.e. dizziness, loss of balance)		*				*		*	
Pain									
Myalgia / joint pain	*	*	*	*		*	*	*	*
Headache / eye pain	*	*	*			*	*	*	*
Abdominal pain								*	*
Neurocognitive deficits									
Memory problems	*	*	*			*	*	*	*
Cognitive difficulties (i.e. 'brain fog', confusion, 'slowness' of thought) also referred to as cognitive dysfunction		*	*		*	*	*	*	*
Poor concentration	*	*	*			*		*	*

Symptom/sign category	CDC Fukuda, 1994[42]	ICC, 2011[16, 17]	Carruthers, 2003[15]	Oxford, 1991[147]	IOM, 2015[59]	NICE, 2007[124]	CDC Holmes, 1988[55]	Jason, 2006[66]	Rowe 2017[140]
Language issues (i.e. dyslexia, word-finding, forgetting what wanted to say)		*	*			*		*	*
Sensory or cognitive overload ('crash' periods)		*	*				*		
Mood									
Mood disturbances				*			*		
Sleep problems									
unrefreshing sleep	*	*	*		*	*		*	*
disturbed sleep patterns		*	*	*			*	*	*
Immunological symptoms									
Low grade fever			*			*	*	*	
Tender lymph nodes	*	*	*			*	*	*	*
Sore throat	*	*	*			*	*	*	*
Susceptibility to infection		*	*						
Chemical hypersensitivity (i.e.to food, allergies)		*	*					*	
General malaise (i.e. flu-like symptoms)						*			
Other systemic symptoms									
Gastrointestinal (i.e. nausea, IBS)		*	*			*			
Genitourinary (i.e. urgency/frequency)		*	*						
Cardiovascular - orthostatic intolerance		*	*		*			*	
Other cardiovascular (i.e. palpitations)		*	*					*	
Respiratory (i.e. sensation of dyspnoea)		*	*					*	
Intolerance of temperature extremes (includes loss of thermostatic stability)		*	*					*	
Marked weight loss								*	
General considerations									

Symptom/sign category	CDC Fukuda, 1994[42]	ICC, 2011[16, 17]	Carruthers, 2003[15]	Oxford, 1991[147]	IOM, 2015[59]	NICE, 2007[124]	CDC Holmes, 1988[55]	Jason, 2006[66]	Rowe 2017[140]
Minimum symptom duration required	6m	NONE	6m(adult) 3m (child)	6m	6m	4m (adult) 3m (child)	6m	3 m	6m
Description of a sudden onset of ME/CFS			*			*	*		
Not life-long				*		*			
Exclusion of differential diagnoses	*	*	*	*		*	*	*	*
Specific physician-conducted tests or objective clinical examination to detect ME/CFS							*		

1.1.5. Economic evidence

The committee agreed that health economic studies would not be relevant to this review question, and so were not sought.

1.1.6. Evidence summary

1.1.6.1. Diagnostic criteria for both adults and children

- Four studies[15, 59, 124, 140] (Carruthers [15, 59, 124, 140]) with serious limitations to very serious limitations reported criteria developed for clinical use. Criteria were broadly overlapping, with all including post-exertional malaise, severe and prolonged fatigue unexplained by activity, cognition difficulties and unrefreshing sleep, although there were differences in whether the symptoms/signs were compulsory for diagnosis. There were also differences in the inclusion of other symptoms/signs such as motor and sensory deficits, pain, immunological and other systemic symptoms, description of a sudden onset, being life-long and exclusion of differential diagnoses. Minimum symptom duration ranged from 4 months to 6 months for adults and 3 months to 6 months for children.
- Three studies[42, 55, 147] (Fukuda [42, 55, 147]) with very serious limitations reported criteria developed for research purposes. All criteria included prolonged fatigue unexplained by activity and myalgia/joint pain and exclusion of differential diagnoses. The only compulsory features were fatigue/fatigability and exclusion of differential diagnoses. Criteria differed on the inclusion of other symptoms/signs such as post-exertional malaise, motor and sensory deficits, other types of pain, neurocognitive deficits, mood, sleep problems, immunological and other systemic symptoms, being life long and specific physician-conducted tests or objective clinical examination to detect ME/CFS. All criteria specified a minimum symptom duration of 6 months.
- Two studies[17, 66] (Carruthers 2011(ICC) [17, 66]) with very serious limitations reported a set of criteria developed for use in both clinical and research settings. The criteria included post-exertional malaise as a compulsory feature, prolonged fatigue unexplained by activity, motor and sensory deficits, pain, neurocognitive deficits, sleep problems, immunological and other systemic symptoms and exclusion of differential diagnoses. There was no minimum symptom duration.

Diagnostic criteria for children

- One study with very serious limitations reported a set of criteria developed for clinical use. The criteria included post-exertional malaise, prolonged fatigue unexplained by activity and impaired function as compulsory features, pain, neurocognitive deficits, sleep problems and immunological symptoms and exclusion of differential diagnoses. The minimum symptom duration was 6 months.
- One study with very serious limitations reported a set of criteria developed for use in both clinical and research settings. The criteria included post-exertional malaise, prolonged fatigue unexplained by activity and sleep problems as compulsory features, motor and sensory deficits, pain, neurocognitive deficits, immunological and other systemic symptoms and exclusion of differential diagnoses. The minimum symptom duration was 3 months.

1.2. The committee's discussion and interpretation of the evidence

This review examines the criteria currently in use in clinical practice and research to assess which of those criteria are most appropriate for suspecting and then establishing an ME/CFS diagnosis for clinical practice.

1.2.1. The outcomes that matter most

This review identified and described the published sets of criteria that have been developed through consensus to establish a diagnosis of ME/CFS. The symptoms and signs within each of the criteria are described and the similarities and differences between the sets of criteria outlined.

The diagnostic criteria have not been evaluated in terms of their measurement validity and accuracy in diagnosing ME/CFS. Without a biomarker it is not possible to definitively know if a person has or does not have ME/CFS. Without such a reference standard (or 'gold standard') it is not possible to assess the measurement validity of the different criteria.

There are published studies that assess how a new set of diagnostic criteria can differentiate between cases and controls; however because the status of cases and controls are based on another set of criteria, this method only measures *agreement* between the different sets of criteria, and not measurement validity. In the absence of a reference standard it can not be assumed previous criteria are superior and it is not possible to assess if the level of agreement between new and previous criteria represents a positive or negative outcome.

Other methods assess the prevalence of ME/CFS measured by a set of criteria, but again these do not establish measurement validity they compare the prevalence of the conditions as described by the criteria. Again, because one set of criteria cannot claim to be more accurate in diagnosing ME/CFS than the others, disagreements in prevalence cannot be extrapolated to differences in measurement validity.

1.2.2. The quality of the evidence

There is no current gold standard for diagnosing ME/CFS so it is not possible to validate the criteria used in different definitions. A pragmatic approach that bypasses the difficulties concerning measurement validity is possible. If the criteria cannot, due to the lack of a reference standard, be shown to be 'correct' or 'not correct', then the second best option is to show that the criteria have been developed using optimal methods. This is because an unbiased, clearly reported, evidence-based and consensus-driven process utilising the expertise of patients, clinicians and researchers is most likely to lead to more clinically useful criteria. This is the basis of the quality criteria used in this review. Quality was measured using a set of quality criteria based on the AGREE II quality criteria, as described in Appendix D.

All of the evidence had serious or very serious limitations, largely a result of lack of methodological rigour, lack of stakeholder involvement and lack of consideration of applicability/implementation of the criteria.

1.2.3. Benefits and harms

This review described the seven diagnostic criteria for adults and two diagnostic criteria for children and young people that met the inclusion criteria set out in the protocol (see Appendix A).

The committee acknowledged there is an ongoing discussion in the ME/CFS community about which diagnostic criteria are best and which should be used in the identification and diagnosis of ME/CFS. The factors influencing these discussions are the broadness of the inclusion criteria, the definition of some of the symptoms, and the usability of the criteria as a clinical tool.

1.2.3.1. Suspecting ME/CFS and making a diagnosis of ME/CFS – description of recommended criteria and committee discussion

The signs and symptoms common to most of the criteria are listed below, the criteria that do not include that sign or symptom is in the brackets:

- Post exertional malaise (not included in the Oxford Criteria) and other severe and prolonged fatigue unexplained by activity
- Pain, specifically joint pain (not included in the IOM) and headache/eye pain (not included in the Oxford Criteria or IOM)
- Cognitive impairment, specifically memory problems (not included in the Oxford Criteria or IOM) and brain fog (not included in the Oxford Criteria)
- Unrefreshing sleep (not included in the Oxford Criteria or the CDC 1998)
- Tender lymph nodes (not included the Oxford Criteria or IOM)

This overview of the criteria fitted with the committee's clinical and/or personal experience about the core features of ME/CFS and increased their confidence in making a recommendation about the signs and symptoms present when ME/CFS should be suspected and diagnosed.

The committee considered the balance between over-diagnosis and missing a diagnosis. Whilst the IOM, 2015 criteria are potentially more encompassing than the ICC, reducing the probability of missing a diagnosis, the IOM criteria are also potentially narrower than some of the other criteria such as the Fukuda, reducing the risk of over-diagnosis. In this way the IOM, 2015 criteria were judged by the committee as allowing a reasonable compromise between over and under inclusion of people within the diagnostic criteria. The committee acknowledged that this judgement was made in the absence of formal measures of accuracy.

The IOM 2015 criteria requires a person has each of the following symptoms for a diagnosis:

- A substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest, and
- Post-exertional malaise, and
- Unrefreshing sleep and
- either cognitive impairment or orthostatic intolerance.

The committee made a consensus decision that the IOM 2015 criteria were a useful set of criteria, having advantages over other criteria in terms of usability (see discussion in the other factors the committee took into account) and an optimum balance of inclusion/exclusion criterion. The committee agreed to use the IOM, 2015 criteria as a basis for their recommendation of when to suspect someone may have ME/CFS. The criteria were modified slightly and this is described below. The committee considered the modifications and clarifications improved the usefulness and usability of the IOM 2015 criteria.

The committee recognised this adds another set of consensus criteria to the literature. The committee noted the evidence calling for clarity over diagnostic criteria and terms used to

describe ME/CFS and the symptoms from the information, education and support for health and social care professionals (see Evidence review B:Information and Support for health and social care professionals) and agreed that it was important to have a set of criteria that is informative and enables health and social care professionals to recognise ME/CFS. The committee decided that it was important to make a research recommendation to develop validated criteria and hoped this research would inform future guidance.

Symptoms such as fatigue and sleep problems are generic to many conditions and the committee considered it was important that there was definition and explanation alongside the recommendation about how these proposed symptoms present in people with ME/CFS and how this may differ from presentations in other conditions. For example, the committee noted that fatigue and sleep problems specific to ME/CFS in adolescents can be difficult to distinguish from fatigue attributed to 'normal' teenager behaviour.

Fatigue

The committee considered that 'fatigue' required precise definition because the same term can potentially be used across a spectrum from a benign physiological response after activity (in well populations) to a disabling mental and physical exhaustion that bears little relationship to the stimulus that precipitated it (in ME/CFS populations).The committee agreed that 'fatigue' as it is commonly used is not a true description of the symptoms in someone with ME/CFS.

The committee considered the wording of the first paragraph of the original IOM criteria, where the effects on function from fatigue are stressed, did not give enough emphasis to the fatigue as the cause of the reduction in function.

The committee discussed the different types of fatigue identified in the ME/CFS literature and their own experiences. There was agreement that there is a marked difference between 'normal tiredness' and the profound fatigue caused by ME/CFS and that the term fatigue does not reflect the actual symptoms that people with ME/CFS experience. Several alternative terms were suggested by the committee members to capture this including; fatiguability, debilitating fatigue, post-exertional exhaustion; post-exertional debility; post-exertional weakness. The committee decided upon 'debilitating fatiguability' with a short explanation in the recommendation clarifying that is not the result of ongoing excessive physical, emotional or mental exertion, and is not substantially alleviated by rest. A further explanation of fatiguability has been added to the terms used in the guideline to provide further support for clinicians.

Post-exertional Malaise

The committee considered the term post exertional malaise (PEM) to be outdated and agreed that the term 'post exertional symptom exacerbation' (PESE) reflects better the interaction with pre-existing symptoms. Some of the committee considered 'malaise' can have the impression of a vague discomfort by people who do not have an understanding of ME/CFS.

The committee considered PESE was a term not often understood by people outside of the ME/CFS community and wanted to clarify how it should be interpreted in a recommendation. The key feature of PESE is that the malaise (extreme fatigue and flu-like symptoms) and other symptoms experienced are not in proportion to the activity that has been done. PESE is often delayed and may be experienced hours or days after the activity took place, the committee were aware of some literature that suggested this is most likely to occur 1-2 days after the exertion. This delay can lead clinicians and people to believe that symptom exacerbations are random and unrelated to a trigger as they do not attribute their worsened

condition to something that may have happened days earlier. The effects of PESE can last for hours, days, weeks or even months. Longer periods of PESE are often referred to as 'crashes' or flares by people with ME/CFS and may precede a sustained relapse.

The committee thought it was important to provide clarity about what is meant by activity in this context. Activity refers to any effort that requires energy expenditure and includes cognitive, physical, emotional and social activity, it is not limited to physical activity. The committee noted that misunderstanding of 'activity' can lead to people with ME/CFS being expected to participate in activities that while are not seen as physically demanding by someone without ME/CFS can have a damaging impact on their energy levels. One example could be engagement in social activity or being in any over stimulating environment. A definition of activity was added to the terms used in the guideline.

Unrefreshing sleep

The committee agreed that sleep difficulties are one of the central features of ME/CFS. As with fatigue and PESE the committee considered that the type of sleep difficulties people with ME/CFS experience are poorly understood. In people with ME/CFS unrefreshing sleep manifests especially as exhaustion, flu-like feelings and stiffness upon waking, and may be caused by broken or shallow sleep, or a reversed sleep-wake cycle. Other manifestations of sleep dysfunction in people with ME/CFS can include insomnia, hypersomnia, , and vivid nightmares. People with ME/CFS can have a full night's sleep but this will not alleviate their fatigue (and other ongoing symptoms) as would be expected in a healthy population.

Cognitive difficulties

The committee noted that cognitive difficulties, such as brain fog, are not a compulsory feature in the IOM, 2015 criteria but as an 'either or' criterion alongside orthostatic intolerance. Based on their experience as this being one of the most commonly reported features of ME/CFS the committee considered cognitive difficulties an essential criterion for suspecting ME/CFS and diagnosis.

Criteria agreed by the committee

On this basis the committee agreed the criteria and recommended that ME/CFS should be suspected in people with these 4 key features:

1. Debilitating fatiguability that is not the result of ongoing excessive physical, emotional or mental exertion, and is not substantially alleviated by rest.
2. Post-exertional symptom exacerbation, which is disproportionate to the amount of exertion (cognitive, physical, emotional and, social), and can be delayed
3. Unrefreshing sleep
4. Cognitive difficulties

These four symptoms were agreed by the committee as the best basis for identifying people with ME/CFS and as essential to a diagnosis of ME/CFS. The committee added further detail into the recommendation clarifying how to recognise these symptoms in people suspected with ME/CFS.

In addition to the four symptoms the committee agreed that as in the IOM 2015 criteria there should be a substantial reduction or impairment in pre-illness levels of function and symptoms should be new and have had a specific onset.

Associated symptoms

In addition to the key features discussed above (debilitating fatiguability, post-exertional symptom exacerbation, unrefreshing sleep and cognitive difficulties) the committee noted that many of the criteria also included symptoms that are commonly experienced by people with ME/CFS. They agreed that while these symptoms were not key to diagnosis they are key to understanding ME/CFS and supporting the management of symptoms. The committee highlighted the following associated symptoms as being particularly important:

- Orthostatic intolerance and autonomic dysfunction, including dizziness; palpitations; fainting; nausea on standing or sitting upright from a reclining position.
- Temperature hypersensitivity resulting in profuse sweating, chills, hot flushes, or feeling very cold.
- Neuromuscular symptoms, including twitching and myoclonic jerks.
- Flu-like symptoms, including sore throat, tender glands, nausea, chills or muscle aches.
- Intolerance to certain foods, alcohol and chemicals.
- Heightened sensory sensitivities, including to light, noise, touch and smell.
- Pain, including on touch, myalgia, headaches, eye pain, abdominal pain or joint pain without acute redness, swelling or effusion.

As discussed above the IOM, 2015 criteria listed orthostatic intolerance alongside cognitive difficulties as an 'either or' symptom for diagnosis. The committee considered that orthostatic intolerance is an important symptom that is often present in people with ME/CFS and can be very debilitating. In the committee's experience recognition of orthostatic intolerance and the appropriate treatment can improve people's functioning (see Evidence review G: non pharmacological management).

Pain and decreased pain threshold, and flu like symptoms were identified in most of the criteria as symptoms for suspecting ME/CFS and diagnosis and the committee agreed they were important to be aware of. In particular, they noted people with ME/CFS often described having flu like symptoms in the initial stages of ME/CFS. The committee agreed that temperature hypersensitivity, neuromuscular symptoms, intolerances and sensory sensitivities were all mentioned to some extent in the criteria and were common symptoms they were aware of.

The committee noted the difficulty in identifying the cause of symptoms in children and young people and commented that symptoms such as abdominal pain or a sore throat are particularly relevant to consider in children and young people as they can localise symptoms to these areas.

1.2.3.2. When to diagnose ME/CFS

The committee agreed that the signs and symptoms for suspecting ME/CFS are the same as those for diagnosing ME/CFS. The confirmation of diagnosis comes with duration of the symptoms and the exclusion of other conditions. The committee emphasised the importance of considering alternative diagnoses, as well as co-existing conditions and comorbidities when assessing a person for ME/CFS (see evidence review G:non pharmacological management on assessments and plans).

<u>Duration of symptoms – suspecting ME/CFS</u>

The committee discussed in depth the complexities around defining a period of time, first of all when ME/CFS should be suspected, and then when it should be diagnosed.

Throughout the evidence reviews (Evidence review A:Information and support for people with ME/CFS, Evidence review B:Information and support for health and social care professionals and evidence review C: Access to care), reports on children and young people and people with severe ME/CFS (Appendix 1 and 2) and Dr Muirhead's expert testimony is the finding that people with ME/CFS experience delays in diagnosis. Early diagnosis is seen as critical to better care and may also improve prognosis. Appropriate advice on activity and rest given in the early stages of ME/CFS is seen as the key to prevent deterioration (see Evidence review E: pre diagnosis strategies). However, what is not clear is at what point ME/CFS should be suspected and then later diagnosed. Based on their experience the committee decided that ME/CFS should be initially suspected in people who have the four key features (debilitating fatiguability post-exertional symptom exacerbation, unrefreshing sleep and cognitive difficulties) for a minimum of 6 weeks in adults and 4 weeks in children and young people. The rationale behind this was that it would be unusual for an acute illness, including a viral illness to persist longer than this with all the symptoms. The committee emphasised it is the combination and interaction of the symptoms that is critical in distinguishing ME/CFS from other conditions and illness. At this point advice on managing symptoms should be given (see Evidence review E: pre diagnosis strategies), in addition to advice children and young people should be referred to a paediatrician for further assessment and investigation of other causes. The committee considered it was important that children and young people with these symptoms did not wait longer to see a paediatrician but they did not consider it necessary they should be referred to a specialist ME/CFS paediatric service until further assessments and investigations had been done.

Duration of symptoms - diagnosing ME/CFS

All the criteria except the ICC criteria included a minimum symptom duration period. All the criteria stated 6 months for an adult except the NICE CG53 criteria which stated 4 months. The minimum duration for children ranged from 3 to 6 months. The committee drew on their experience and the evidence reviews on access to care (report C)and agreed that ME/CFS should be diagnosed in people with the key features (debilitating fatiguability, post-exertional symptom exacerbation, unrefreshing sleep and cognitive difficulties) for 3 months. The committee reflected that the evidence across the guideline (Evidence review A:Information and support for people with ME/CFS, Evidence review B:Information and support for health and social care professionals and evidence review C:Access to care), reports on children and young people and people with severe ME/CFS (Appendix 1 and 2) and Dr Muirhead's expert testimony) highlighted the lack of knowledge and education that health and social care practitioners have about ME/CFS. This lack of knowledge is perceived to underpin a lack of confidence in recognising and diagnosing ME/CFS resulting in delays to diagnosis. The committee agreed that as primary healthcare professionals are the most likely professionals that people with suspected ME/CFS will initially meet it was important to make a recommendation that they should have training relevant to their role (for example, in identifying ME/CFS).

The committee agreed that although a 6-month delay to diagnosis is built into the IOM criteria, the criteria could be safely amended by the reduction of this delay period to 3 months. It was agreed that the function of a delay is partly to reduce the number of misdiagnoses through allowing short-lived fatigue to be excluded. In addition to not being disadvantageous, removal of the delay was seen as beneficial, as this might facilitate earlier management and potentially allow improvement in longer term outcomes.

There are concerns with both a false positive and false negative diagnosis of ME/CFS. Both scenarios may lead to improper interventions, withholding of treatment and a prognosis for a disease or condition they do not have. The committee emphasised the importance of identifying and excluding other conditions, and that these should be appropriately investigated in people with suspected ME/CFS.

The committee were aware of people who had been wrongly diagnosed with ME/CFS and as a result had not received appropriate treatment for other conditions. To mitigate the risk of missing an alternative diagnosis, it is important that clinicians consider differential diagnoses carefully, and continue to monitor people with suspected ME/CFS for the emergence of new symptoms which could indicate an alternative diagnosis, especially when symptoms may overlap or be confused with those with ME/CFS. It is also important to recognise that a positive or suspected ME/CFS diagnosis does not mean someone does not have or could not develop a co-existing condition or a co-morbidity. If a clinician has any concerns about interpreting signs and symptoms they should consider referral to the relevant specialist.

Co-existing conditions and differential diagnoses are discussed further in the 'other factors the committee took into account' section below.

1.2.3.3. Unpredictability and severity of symptoms

One of the complexities of identifying ME/CFS is the fluctuating and unpredictable nature of the symptoms. Symptoms follow a characteristic pattern of variability and can develop over time. The committee noted that most people with ME/CFS have a fluctuating course, where symptoms wax and wane over the course of the day or longer. Fluctuations can be affected by any activity, infections, vaccinations, stress, food intolerances, temperature extremes and any other environmental stimuli.

The committee also discussed that when a patient first presents to a clinician they are unlikely to be experiencing their symptoms at the worst level. Severe physical fatigue may mean that someone is unable to physically visit a clinic and cognitive difficulties may mean they are less able to explain their symptoms to a clinician. Also it can be difficult to judge severity when clinicians do not usually see the result of overexertion, especially if they do not understand PESE. The committee emphasised it was important for clinicians to be aware that a patient in their surgery is likely to be better than they are at other times, and to bear this in mind when making judgements about severity. To help the clinicians to gain a more complete picture of the person's condition they should ask information about their symptoms over a longer course of time.

A recommendation was included to raise awareness about the fluctuating nature of ME/CFS and how this can mean that people can present differently throughout their illness. The committee noted that the unpredictability of symptom severity prevents planning ahead and reliability, even in the immediate- and short-term (for example, over the next couple of hours), and this may impact on attendance at work, education or training, social events, or vital appointments. This important information should be acknowledged when considering the impact of the illness on a person's life and any support they may require (for example, in applications and assessments for social care support, benefits, education and adjustments) (see evidence review C:Access to care).

1.2.3.4. Children and young people

The committee acknowledged that the majority of the evidence identified in this report was conducted in adult populations with the exception of the criteria developed by the International Association of Chronic Fatigue Syndrome Paediatric Case definition Working group [66] and International Writing Group for Paediatric ME/CFS [140]. They observed that these two criteria identified the same key symptoms as those identified in the adult criteria. The committee agreed that on this basis and reflecting on their own knowledge and experience the majority of the recommendations on suspecting and diagnosing ME/CFS could be generalised to children and young people. The committee made additional recommendations for referral and diagnosis and communication of symptoms in children and young people.

<u>Referral to a paediatrician</u>

The committee discussed the importance of recognising and referring children and young people with suspected ME/CFS as early as possible to a paediatrician and after further assessment and investigation to a paediatrician that has expertise in ME/CFS. They took into account their own experience and evidence from the report on children and young people.

The journey to diagnosis was identified as one of the key themes in the report findings. The participants describe their symptoms initially as 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 and they recognised the uncertainty and anxiety for the child, young person and their families that can result from a long wait for referral and delays to diagnosis. The committee estimated that currently time to referral and before a diagnosis is confirmed by a paediatrician can be up to 6 months and some young people in the report delays of up to 18 months. As stated above the delay is accompanied by a lack of support and advice. The committee commented on the devastating impact this can have on a child or young person's education and training and they were aware that ME/CFS is one of the most common causes of long-term school absence.

In order to address this and reduce the time waiting for a referral and diagnosis the committee recommended that ME/CFS should be suspected in a child or young person who had symptoms for a minimum of 4 weeks. This is two weeks less than adults in the recognition that it is unusual for children to be acutely ill for this length of time. This approach avoids the delays in diagnosis and the committee have made recommendations about the management of symptoms in people suspected ME/CFS and recommendations supporting education and training in children and young people. The committee noted that in their experience using a provisional diagnosis of suspected ME/CFS was beneficial and enabled children, young people and their families to access support in continuing their education before a diagnosis had been made.

The committee acknowledged there is a risk that an provisional diagnosis of suspected ME/CFS could be wrong, but they agreed none of the recommendations in the guideline before diagnosis are likely to cause harm. The recommendations are clear there should be review of symptoms and that when suspecting ME/CFS the possibility of another condition should not be excluded. This the committee agreed addressed and outweighed the impact of delayed and late diagnosis.

Description of symptoms by children

The committee discussed the difficulty that children and young people can have in describing their symptoms. They took into account their own experience and evidence from the children and young people report. The committee highlighted that children may experience difficulty articulating their symptoms either because they regard them as normal as a result of experiencing them for a long time or because they lack the vocabulary to describe them; and that clinicians should be aware of that they may find consultations difficult after being in isolation or after previous negative experiences of not being believed by clinicians , teachers and peers. One participant in the children and young people report commented that being in a medical appointment without their mother was scary.

While recognising that it is not unusual for children and young people to have difficulty in describing how they feel the committee considered it very important this was acknowledged

here considering that it is the combination of symptoms, clinical examination and history-taking are vital to the diagnostic process.

1.2.4. Cost effectiveness and resource use

It was agreed by the committee should not be sought for this question.

The committee's criteria for diagnosing ME/CFS are more restrictive than in the previous NICE guideline (CG53), since patients are required to have all the following: debilitating fatiguability, post-exertional symptom-exacerbation, unrefreshing sleep and cognitive difficulties. However, compared with CG53, the duration of symptoms required for diagnosis is shorter (3 months). This is to allow faster access to appropriate care for those that clearly meet the diagnostic criteria. In line with the committee's experience, expert witness testimony and the views and experiences of people with ME/CFS emerging from qualitative reports, it is very common for people with ME/CFS to experience delays in diagnosis. This negatively impacts not only their physiological and psychological well-being, but is also likely to influence prognosis, as diagnostic delay leads to delayed management advice and often to deterioration of symptoms. An earlier diagnosis provides a window for early intervention that can be critical to better care which by preventing the deterioration of symptoms can reduce the long-term costs involved in the care of people who become severely affected and those who do not improve over time.

The committee have recommended that diagnosis is confirmed by a specialist team. This has been informed by the qualitative evidence included in other reviews for this guideline, that describe the barriers people have faced in reaching a diagnosis. In the case of children, referral should be sooner than 3 months to ensure that there is not significant damage to the child's education and development.

The net resource impact of these could mean a shift of resources rather than an increase. The main outcome should be earlier access to appropriate care, which should improve efficiency by avoiding unnecessary and harmful treatment.

1.2.5. Other factors the committee took into account

Usability of the criteria

The committee acknowledged that many different case definitions exist with some being developed for use in clinical practice and others for research. In this review four of the criteria identified were developed for use in a clinical context [15, 59, 124, 140], three were developed for research purposes[42, 55, 147] and two were developed for use in both settings.

The committee noted that some of the criteria are harder to use than others and ease of use is important to increase confidence in clinicians that are not familiar with ME/CFS. For clinical practice criteria that are simple and not time consuming are likely to be most helpful. The committee agreed that the IOM, 2015 criteria were clinical criteria developed to facilitate clinical diagnosis and are user-friendly to clinicians because of their relative brevity, simplicity and clarity of symptoms. The IOM, 2015 criteria were regarded as easier to use, needing less specialist knowledge and experience of treating people with ME/CFS, compared to more complex criteria such as the ICC and therefore particularly suitable for non-specialists. The quality assessment rated them as partially meeting the domain evaluating applicability, due to lack of consideration of potential resource implications not being reported, however it was noted that all other items within this domain, including consideration of barriers and facilitators to implementation, strategies to improve uptake and monitoring of the impact were met.

The committee discussed that in practice no one criteria is used clinically with a 'mix and match' approach being used alongside clinical experience. For this reason none of the criteria were seen by the committee as having the added advantage of usability when considering if any should be used over the others in clinical practice.

Symptom assessment questionnaires

The committee noted as well as the difficulties in defining a set of diagnostic criteria there is no standardised way of symptomology assessment. The committee discussed the use of symptom assessment questionnaires and in particular the DePaul Symptom Questionnaire (DSQ) developed to assess the symptomatology and case definition of people with ME/CFS. This tool was identified in the literature search for the diagnostic criteria but did not meet the inclusion criteria as it was not clear from the original publication of the criteria upon which it was based what methods were used to develop them, i.e. whether or not they were developed though consensus/guidelines.

Differential and coexisting diagnosis

The committee discussed that the non-specific nature and common presentation of some of the symptoms (for example, cognitive difficulties such as brain fog) that are characteristic of ME/CFS make it difficult to diagnose and initially to distinguish from other conditions. This is compounded by HCPs lack of understanding about the symptoms and the relationship with other conditions (for example, fatigue and depression). This has led to misdiagnosis, missed diagnosis, delays in the diagnosis of ME/CFS and of other conditions. This was highlighted in the evidence review B:Information for health and social care professionals

As noted above the committee agreed it is important that clinicians when suspecting ME/CFS in a person also consider the possibility of an alternative explanatory diagnosis or a co-existing condition. The IOM 2015, states that, 'the presence of other illnesses should not preclude patients from receiving a diagnosis of ME/CFS (SEID) except in the unlikely event that all symptoms can be accounted for by these other illnesses." The committee were clear that when ME/CFS is suspected that the possibility of another condition should not be excluded, baseline investigations to exclude other diagnoses should be carried out and advice from a specialist in the appropriate topic should be sought if there is any uncertainty.

The committee noted that the previous NICE guideline (CG53) provided a list of exclusionary tests (for example, tests for differential diagnoses such as multiple sclerosis) to carry out as part of the diagnostic process. The committee agreed that to include a current list of tests to test for other conditions each test would require an evidence review of its diagnostic accuracy for the specific condition.

However the committee noted that because of the difficulties people with ME/CFS have reported with misdiagnosis, missed diagnosis, delays in diagnosis in ME/CFS and of other conditions it was important to raise awareness of the clinical conditions that may produce similar symptoms. The committee based their decision making on the conditions from the literature from the diagnostic criteria review. Any tests are then specific to the condition suspected by the clinician based on the person's symptoms.

Eight of the 9 criteria in the review identified exclusion of other conditions through a process of differential diagnosis. While it is possible for ME/CFS to occur concurrently with other disorders, it is important to be aware that many medical conditions are associated with fatigue and may share additional features with the criteria for ME/CFS.

The committee took the view that an exhaustive list of all possible conditions which might be considered was not possible, nor was it appropriate to provide advice on these conditions in this guideline, where there is relevant NICE guidance it is referenced in the recommendations.

Examples are as follows:

- Endocrine, nutritional and metabolic disorders: including thyroid disorders, primary and secondary adrenocortical insufficiency, Haemochromatosis, chronic kidney disease, vitamin deficiencies
- Genitourinary system disorders: chronic bladder infection, chronic vulvar pain
- Auto-immune and inflammatory disorders: including primary Raynaud's, systemic lupus erythematosus, Sjogren's syndrome, vasculitis, inflammatory bowel disease, coeliac disease, primary biliary cirrhosis, sarcoidosis, kidney disease; endometriosis
- Infections and infection- related disorders: including HIV, chronic viral hepatitis, tuberculosis, Lyme disease and post-Lyme syndrome, other chronic infections including those rare in the UK. Also, recurrent infection associated with immune deficiency disorders
- Neurological disorders: including multiple sclerosis and myasthenia gravis
- Cardiorespiratory disorders: including cardiac failure, chronic obstructive pulmonary disease, respiratory failure, chronic endocarditis
- Haematological disorders: anaemias, lymphoma, chronic leukaemia, myeloma
- Malignant disease: particularly those cancers which are often not easy to detect such as ovarian carcinoma
- Sleep-wake disorders: including obstructive sleep apnoea and narcolepsy
- Other chronic pain and multisystem disorders: including fibromyalgia and hypermobility spectrum disorder.
- Iatrogenic conditions: particularly side effects of medications used for chronic pain.

1.2.5.1. Development of criteria for research or clinical use

Four of the criteria identified were developed for use in a clinical context, three were developed for research purposes and two were developed for use in both settings.

The criteria developed for research appear to be broader than the criteria developed for clinical use. For example, the Oxford Criteria have more inclusive criteria than the ICC and the IOM 2015 has the least inclusive criteria. The committee noted that this variance results in diagnostic unreliability, with the ICC criteria identifying a smaller subset of people with ME/CFS with more severe symptoms than the Fukuda criteria.

When broader criteria are applied more people are diagnosed with ME/CFS, reducing the chances of a missed diagnosis of ME/CFS but increasing the number of false diagnoses. In clinical practice this may appear a conservative strategy ensuring the number of people with a missed diagnoses is low. However, there is the possibility that there are a number of people with another illness that receive a false positive diagnosis. The clinical implications of this can be serious with people not receiving appropriate treatment for an undiagnosed condition or a treatments being implemented that are not targeted to any one condition.

Similarly using broad diagnostic criteria to recruit to a research study will have a larger data sample set. As a result the population could be heterogeneous and may not only be comprised (in the case of this guideline) of a ME/CFS population. Here specificity, not sensitivity, of diagnostic criteria is more important in ensuring the validity of research studies with true cases recruited.

The committee discussed the distinction between research and clinical criteria and the implications of this for the diagnosis of ME/CFS and the impact on other areas of the guideline when interpreting the evidence. If interventions are based on evidence that include other populations (for example using the broader criteria) this could result in the implementation of interventions that are potentially ineffective for subsamples of patients.

The committee noted that the majority of the studies conducted in this area have recruited participants using criteria that do not include post exertional malaise/post-exertional symptom exacerbation as key inclusion criterion and include broader interpretations of fatigue alongside PEM/PESE. Arguably this has resulted in heterogeneous study populations with subsamples of people with different conditions. It is difficult to know the number of people that have PEM/PESE and are considered in the tighter criteria to have ME/CFS. The committee agreed this proposed some difficulties in interpreting evidence that did not include PEM/PESE as a key diagnostic criterion with the potential of an overestimation or underestimation of association or effect. As a result the committee agreed to consider the evidence based on inclusion criteria that did not include PESE as a compulsory feature for diagnosis as 'indirect', on the basis that it was difficult to be sure if the population consisted only of people with ME/CFS. There is further discussion in the evidence reviews on management of ME/CFS (reports G and H) and how this impacts on the quality assessment and interpretation of the evidence.

2. Diagnostic tests

2.1. Review question

What is the diagnostic accuracy of specific tests to identify ME/CFS in people with suspected ME/CFS?

2.1.1. Introduction

This review aims to identify up to date evidence in relation to tests which may help to identify ME/CFS, and to assess which of these may be useful to incorporate into clinical practice.

2.1.2. Summary of the protocol

For full details see the review protocol in Appendix A.

Table 5: PICO characteristics of review question

Population	Adults, children and young people who are suspected of having ME/CFS by their primary clinician, but who are yet to be formally diagnosed.
Target condition	ME/CFS
Index tests	• 2-day cardiopulmonary exercise testing • grip strength • IMS • cytokine profile • ESR • mitochondrial function tests • postural hypotension test CRP
Reference standard **Comparator**	Clinical diagnosis of ME/CFS <u>Diagnostic RCT</u> Any testing strategy compared with any other

Statistical measures
 	
Outcomes
	<u>Measures of diagnostic accuracy</u>
	• Sensitivity
	• Specificity
	• Area under the curve
	• Likelihood ratios
	• Predictive values
	<u>Diagnostic RCT</u>
	CRITICAL
	• Mortality
	• General symptom scales (any validated scales). For example:
	  ○ De Paul Symptom Questionnaire
	  ○ Self-Rated Clinical Global Impression Change Score
	• Fatigue/fatiguability (any validated scales). For example:
	  ○ Chalder fatigue Scale
	  ○ Fatigue Severity Scale
	  ○ Fatigue Impact scale
	• Physical functioning (any validated scales). For example:
	  ○ SF36 physical function
	  ○ SF36 PCS

	• Cognitive function (any validated scales). For example:
	  ○ MMSE
	• Psychological status (any validated scales). For example:
	  ○ Hospital Anxiety and Depression Scale
	  ○ 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
	
	IMPORTANT OUTCOMES:
	• Care needs
	• Impact on families and carers
	
	•

Study design	Diagnostic accuracy Single gate cross-sectional study designs will be included in the accuracy review. Two gate study designs will be excluded from the accuracy review Diagnostic RCT RCTs will be prioritised for test and treat comparisons

2.1.3. 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.

2.1.4. Effectiveness evidence

2.1.4.1. Included studies

No relevant studies were identified.

See also the study selection flow chart in Appendix C and study evidence tables in Appendix E.

2.1.4.2. Excluded studies

See the excluded studies list in Appendix H.

2.1.5. Summary of studies included in the effectiveness evidence

No relevant studies were identified.

2.1.6. Summary of the effectiveness evidence

No evidence was identified.

2.1.7. Economic evidence

2.1.7.1. Included studies

No health economic studies were included.

2.1.7.2. 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.

2.1.7.3. Unit costs

Most test costs are not routinely recorded but here is some information that might help to indicate the approximate cost of the tests in the review protocol.

Blood tests

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are routine tests of inflammatory response. In the NICE Multiple Sclerosis guideline, a few trusts were surveyed and the laboratory cost of a CRP varied from £3.03 to £9.68.

Cytokine profile, Immunosignaturing and mitochondrial function tests (ATP profile) are not used routinely and so are likely to be a bit more costly.

Other tests

The cost of a cardiopulmonary exercise testing (CPET) is submitted by NHS Trusts (by specialty) as part of the NHS reference costs. The average cost was £160 in 2017-18 (n=34,040). However, this did vary by specialty. For example, it was £104 for cardiology and £212 in respiratory medicine. For a 2-day CPET, required to confirm post-exertional malaise, one would expect the cost to be double that of a single CPET.

Postural hypotension can be confirmed by measuring a person's blood pressure after they have been lying down, and again after standing. If this were to take 10 minutes of a practice nurse’s time then this would cost about £6 a test.

Grip strength can be measured with a hand dynamometer, which can be purchased at a cost of £149-£532, according to the NHS supply chain catalogue. This is for use multiple times and hence the cost per patient could be low if it was in routine use.

General considerations

Tests that are higher cost might still be cost effective or even cost saving overall, if they result in an improvement in management.

2.1.8. Evidence statements

2.1.8.1. Effectiveness

- No relevant published evidence was identified.

2.1.8.2. Economic

- No relevant economic evaluations were identified.

2.2. The committee's discussion and interpretation of the evidence

2.2.1. The outcomes that matter most

Diagnostic RCT

Mortality, quality of life, general symptom scales, fatigue/fatigability, physical function, cognitive function, psychological status, pain, sleep quality, treatment-related adverse events, activity levels, return to school/work and exercise performance measures were considered by the committee to be critical outcomes for decision making.

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 reflecting the effectiveness of an intervention.

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.

No RCT evidence was identified.

Diagnostic accuracy

The outcomes were sensitivity and specificity. The committee prioritised sensitivity over specificity on the basis that at this early point in the diagnostic process, it is of greater importance to avoid false negative results and excluding people from a diagnosis. The committee acknowledged that a false positive result could result in a delayed alternative diagnosis for some people.

No diagnostic accuracy evidence was identified.

2.2.2. The quality of the evidence

No evidence was identified in the review

2.2.3. Benefits and harms

Tests

The committee acknowledged the lack of evidence for any tests to diagnose ME/CFS. Therefore, no recommendations were made for any specific tests.

The committee were aware of people being offered tests to diagnose ME/CFS and being encouraged to pay for tests that were not proven to be useful. The committee agreed it was important that people should be aware there are no diagnostic tests currently available and drafted a recommendation making this clear. The committee made a recommendation that people presenting with possible symptoms of ME/CFS should be told that there is no diagnostic test for ME/CFS and it is recognised on clinical grounds alone. In line with this an

assessment should include a comprehensive clinical history, a physical examination, psychological wellbeing.. The committee agreed that in this context, there are no tests to replace clinical judgement and that thorough clinical examination and history-taking are vital to the diagnostic process.

The committee identified 2-day cardiopulmonary exercise testing, grip strength, immuno-signature, cytokine profile, erythrocyte sedimentation rate, mitochondrial function tests, postural hypotension test and C-reactive protein as potential diagnostic tests. These tests were considered to be emerging areas of research that have been identified as potentially showing differences in people with diagnosed ME/CFS compared to people without ME/CFS. The committee noted that the review provided an indication of the absence of evidence rather than of evidence of absence. The committee decided to make a research recommendation to help identify effective diagnostic tests for ME/CFS that will facilitate early diagnosis and potentially lead to better outcomes for people with ME/CFS. They hoped this research would inform future guidance.

2.2.4. Cost effectiveness and resource use

There were no published economic evaluations of testing for ME/CFS.

Since there was not good quality evidence of clinical effectiveness of testing strategies or of diagnostic accuracy, the cost effectiveness of specific tests is uncertain.

Therefore, the committee did not recommend testing for ME/CFS. Patients will require a physical assessment and full history to assess whether they meet the diagnostic criteria.

2.2.5. Other factors the committee took into account

Testing for viruses

The committee discussed that viral infections are often described as a potential trigger of ME/CFS and could therefore constitute a useful pre-diagnosis indicator. The committee noted that in its initial stages, ME/CFS can often feel like having a virus one does not fully recover from. Experience from the committee suggested that this feeling can continue and flares of symptoms can feel like a resurgence of a virus. It was discussed that the illness may be caused by the physiological stress response elicited by infection and not by the virus. The committee were aware of a body of epidemiological literature examining the association between viral infection such as Epstein-Barr and glandular fever and the development of ME/CFS. It was noted that these studies would not meet the review protocol because they were based on a different population, i.e. those with viral infection rather than those suspected of having ME/CFS. The committee noted that no single test can identify all viral infections and specific viruses have to be tested for in order to detect their presence, which would be likely to complicate the diagnostic process.

The committee agreed the importance of performing relevant tests for differential diagnoses, both pre- and post-diagnosis of ME/CFS. It was considered that new symptoms can develop after a diagnosis and that these should still be fully investigated rather than immediately attributed to ME/CFS. During investigation of new symptoms, both differential and comorbid diagnoses should be considered where appropriate. A recommendation was made to remind clinicians that while waiting for diagnosis of ME/CFS to be confirmed they should continue with any tests needed to exclude other conditions and explain to people this does not affect their provisional diagnosis of ME/CFS.

3. Clinical signs and symptoms

3.1. Review question

What are the predictive accuracies of specific clinical symptoms/signs to identify people who will subsequently be given a clinical diagnosis of ME/CFS?

3.1.1. Introduction

This review aims to identify up to date evidence in relation to symptoms and signs which may help to identify ME/CFS early, and to assess which of these may assist in making a clinical diagnosis.

3.1.2. Summary of the protocol

For full details see the review protocol in Appendix A.

Table 6: PICO characteristics of review question

Population	Adults, children and young people who are suspected of having ME/CFS by their primary clinician, but who are yet to be formally diagnosed.
Target condition	ME/CFS
Index tests (signs/symptoms)	• cognitive dysfunction/difficulties • post exercise malaise/post exertional symptom exacerbation • severe fatigue after minimal mental or physical effort • sleep disorders • sensitivity to sound or light • gastrointestinal problems (such as nausea or IBS)
Reference standard	Clinical diagnosis of ME/CFS
Statistical measures [or] Outcomes	• Sensitivity • Specificity • Area under the curve • Likelihood ratios • Predictive values
Study design	Prospective and retrospective longitudinal cohort studies, that evaluate the predictive accuracy of signs/symptoms.

3.1.3. 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.

3.1.4. Effectiveness evidence

3.1.4.1. Included studies

One study was included in the review;[82] this is summarised in Table 7 below. Evidence from this study is summarised in the clinical evidence summary below (Table 8).

See also the study selection flow chart in Appendix C, study evidence tables in Appendix E, and forest plots in Appendix F.

3.1.4.2. Excluded studies

See the excluded studies list in Appendix H.

3.1.5. Summary of studies included in the effectiveness evidence

Table 7: Summary of studies included in the evidence review

Study	Population	Target condition	Index test (signs/symptoms)	Reference standard	Comments
Jason 2011[82]	N=108 People from a random community sample who screened positive for CFS-like illness on the *CFS Screening Questionnaire*	CFS	Other diagnoses: Muscle weakness Insomnia Hypersomnia Irritable bowel syndrome Fukuda symptoms: Unrefreshing sleep Impaired memory or concentration Post-exertional malaise	Diagnosis of CFS at 10 years by a team of physicians with access to all information gathered on each participant during each of the phases of the study.	During 'wave 1' of the study, people who screened positive for CFS-like illness received a series of baseline 'index tests' via a structured psychiatric interview, medical history interview and complete medical examination. During 'wave 2', 10 years later, they were reassessed and categorised as CFS, idiopathic chronic fatigue, exclusions or controls by a team of physicians – this diagnosis was the 'reference standard'. The study reported the percentage of people in each diagnostic category who were positive for signs and symptoms at baseline. For the purposes of this review, sensitivity and specificity was calculated by cross-tabulating (in 2x 2 tables) index test +ve/-ve and reference standard +ve/-ve. Limitations: - those who were too ill to speak on the phone were excluded at initial screening - index tests informed the final diagnosis - high attrition rate (50%)

Study	Population	Target condition	Index test (signs/symptoms)	Reference standard	Comments
					- 10-year gap between index test and reference standard

See Appendix E for full evidence tables.

3.1.6. Summary of the effectiveness evidence

Table 8: Clinical evidence summary: clinical signs/symptoms to predict later diagnosis of ME/CFS

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Muscle weakness to predict later diagnosis of ME/CFS							
1 prospective cohort study	103	Very serious[1]	Not detected	Not serious	Very serious[2]	Sensitivity=0.77 (0.55-0.92)	VERY LOW
		Very serious[1]	Not detected	Not serious	Serious[2]	Specificity=0.41 (0.30-0.52)	VERY LOW
Insomnia to predict later diagnosis of ME/CFS							
1 prospective cohort study	106	Very serious[1]	Not detected	Not serious	Serious[2]	Sensitivity=0.52 (0.31-0.73)	VERY LOW
		Very serious[1]	Not detected	Not serious	Serious[2]	Specificity=0.55 (0.44-0.66)	VERY LOW
Hypersomnia to predict later diagnosis of ME/CFS							
1 prospective cohort study	106	Very serious[1]	Not detected	Not serious	Not serious	Sensitivity=0.30 (0.13-0.53)	LOW
		Very serious[1]	Not detected	Not serious	Not serious	Specificity=0.61 (0.50-0.72)	LOW
Irritable bowel syndrome to predict later diagnosis of ME/CFS							
1 prospective cohort study	106	Very serious[1]	Not detected	Not serious	Not serious	Sensitivity=0.22 (0.07-0.44)	LOW
		Very serious[1]	Not detected	Not serious	Serious[2]	Specificity=0.86 (0.76-0.92)	VERY LOW
Unrefreshing sleep to predict later diagnosis of ME/CFS							
1 prospective cohort study	104	Very serious[1]	Not detected	Not serious	Serious[2]	Sensitivity=0.87 (0.66-0.97)	VERY LOW
		Very serious[1]	Not detected	Not serious	Not serious	Specificity=0.31 (0.21-0.42)	LOW
Impairment of memory/concentration to predict later diagnosis of ME/CFS							
1 prospective cohort study	105	Very serious[1]	Not detected	Not serious	Serious[2]	Sensitivity=0.83 (0.61-0.95)	VERY LOW
		Very serious[1]	Not detected	Not serious	Serious[2]	Specificity=0.41 (0.31-0.53)	VERY LOW
Post-exertional malaise to predict later diagnosis of ME/CFS							

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
1 prospective cohort study	106	Very serious[1]	Not detected	Not serious	Serious[2]	Sensitivity=0.50 (0.29-0.71)	VERY LOW
		Very serious[1]	Not detected	Not serious	Serious[2]	Specificity=0.57 (0.46-0.68)	VERY LOW

[1] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.*

[2] *The evidence was downgraded by 1 increment if the confidence interval crossed 1 decision threshold and downgraded by 2 increments if the confidence interval crossed 2 decision thresholds.*

3.1.7. Economic evidence

3.1.7.1. Included studies

No health economic studies were included.

3.1.7.2. 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.

3.1.8. Evidence statements

3.1.8.1. Effectiveness

- No relevant published evidence was identified.

3.1.8.2. Economic

- No relevant economic evaluations were identified.

3.2. The committee's discussion and interpretation of the evidence

3.2.1. The outcomes that matter most

The outcomes were sensitivity and specificity. The committee prioritised sensitivity over specificity on the basis that at this early point in the diagnostic process, it is of greater importance to avoid false negative results and excluding people from a diagnosis.

One prospective cohort study was included.

3.2.2. The quality of the evidence

Evidence for the accuracy of muscle weakness, insomnia, hypersomnia, irritable bowel syndrome, unrefreshing sleep, impairment of memory/concentration and post-exertional malaise for predicting later diagnosis of ME/CFS was based on a single study and was of very low quality. This was due to risk of bias, imprecision and methodological limitations.

The signs and symptoms examined in this review are included in various existing criteria used to diagnose ME/CFS and informed the eventual diagnosis (reference standard), which meant that associations were potentially confounded. The period between measurement of the index tests (signs/symptoms) and the reference standard was of a long duration (10 years), during which some people moved out of one diagnostic category in to another. There was a high rate of attrition and differences between diagnostic groups in the number of people followed up. These factors, combined with the uncertainty around the sensitivity and specificity estimates reduced the committee's confidence in the evidence.

The committee acknowledged that the study was a natural history study which was not designed to test the diagnostic accuracy of tests/signs/symptoms. Therefore, whilst technically it met the inclusion criteria and the results were interesting, it did not provide sufficient evidence upon which to base any recommendations.

3.2.3. Benefits and harms

The sign/symptom with the highest sensitivity was unrefreshing sleep, followed by impairment of memory/concentration. However, these signs/symptoms also had the lowest specificity, indicating a high proportion of false positive results. The committee considered this as well as the very low quality of the evidence and decided that there was insufficient evidence to make a recommendation for prioritisation for early pre-diagnosis management based on any particular signs/symptoms alone. The committee highlighted that each sign/symptom in isolation is of low predictive value but it is the combination of them that is of importance in a clinical setting.

Ideally evidence would have been identified that confirmed the inclusion of symptoms in the recommended diagnostic criteria. Despite this uncertainty about which of the signs and symptoms should be prioritised for diagnosis the committee agree that it is important to have a set of criteria that include the signs and symptoms commonly agreed to be features of ME/CFS (as outlined above in the discussion of the diagnostic criteria).

The committee noted the lack of good quality evidence on specific signs or symptoms to predict a later diagnosis of ME/CFS. The committee discussed the key symptoms which should prompt suspicion of ME/CFS (see diagnostic criteria section above) and agreed that it is a combination of these symptoms (as well as the overall clinical picture), rather than a specific sign or symptom that is important.

3.2.4. Cost effectiveness and resource use

There were no relevant published economic evaluations.

Appendices

Appendix A – Review protocols

Review protocol: diagnostic criteria

0.	PROSPERO registration number	
1.	Review title	In people with suspected ME/CFS, what are the criteria used to establish a diagnosis?
2.	Review question	In people with suspected ME/CFS, what are the criteria used to establish a diagnosis?
3.	Objective	To identify and describe the existing diagnostic criteria 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 Searches will be restricted by: • English language Other searches:

		• None 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 suspected of having ME/CFS.
7.	Intervention/Exposure/Test	Any diagnostic criteria for ME/CFS based on consensus development by an expert group.
8.	Comparator/Reference standard/Confounding factors	NA – this is a descriptive review
9.	Types of study to be included	-Articles and Review papers defining or describing existing diagnostic criteria for ME/CFS -Consensus based guidelines resulting from multidisciplinary/professional agreement defining or describing existing diagnostic criteria for ME/CFS. -Consensus based guidelines that are publicly available or due to be published resulting from multidisciplinary/professional agreement defining or describing existing diagnostic criteria for ME/CFS identified through a call for evidence.

10.	Other exclusion criteria	Exclude: Data defining and describing existing diagnostic criteria for ME/CFS in papers that have not been published in a peer-reviewed journal Non-English language studies.
11.	Context	N/A
12.	Primary outcomes (critical outcomes)	NA (descriptive)
13.	Secondary outcomes (important outcomes)	NA
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of these potentially eligible studies will be retrieved and assessed in line with the criteria outlined above. A standardised form will be used to extract data from the included studies (see Developing NICE guidelines: the manual section 6.4). Data extraction will be independently quality assured by a second reviewer, discrepancies will be identified and resolved through discussion (with a third party where necessary).

15.	Risk of bias (quality) assessment	We will use a custom-made quality checklist adapted from AGREE II to critically appraise individual studies. **Criterion Description of quality checklist** <u>Transparency</u> There is a detailed description of how the criteria were formed, with details given of methodology used; for example, the methods for achieving consensus are clearly described. <u>Appropriate development group</u> The development group is made up of experts from a variety of specialisms and viewpoints, and also comprises patients and/or their family members or carers <u>Evidence based</u> A systematic literature review was undertaken that has helped to inform the criteria <u>Consultancy</u> The criteria are sent out for wider consultation from stakeholders before the final criteria are passed Studies are graded as: No serious limitations: all four criteria met/ (two criteria met and) two criteria met partially/ (three criteria met with) only one criterion not met; Serious limitations: limitations across at least three criteria with no more than three criteria not met ; Very serious limitations: all four criteria not met
16.	Strategy for data synthesis	Descriptive
17.	Analysis of sub-groups	<u>Stratification:</u> Adults (<u>≥</u>18), Children (<18)

		<u>Subgroups to investigate if heterogeneity is present:</u> NA		
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	02/01/2018		
22.	Anticipated completion date	22/08/2019		
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: [NICE guideline webpage].
29.	Other registration details	N/A
30.	Reference/URL for published protocol	
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. [Add in any additional agree dissemination plans.]
32.	Keywords	Diagnosis, hypertension, high blood pressure
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

1 **Review protocol: diagnostic test accuracy**

0.	PROSPERO registration number	
1.	Review title	What is the diagnostic accuracy of specific tests to identify ME/CFS in people with suspected ME/CFS?
2.	Review question	What is the diagnostic accuracy of specific tests to identify ME/CFS in people with suspected ME/CFS?
3.	Objective	To identify tests that can diagnose 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 Searches will be restricted by: • English language Other searches: • None

		The searches may be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion if relevant. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	ME/CFS
6.	Population	Adults, children and young people who are suspected of having ME/CFS by their primary clinician, but who are yet to be formally diagnosed.
7.	Intervention/Exposure/Test	A prioritised list of tests was decided by the GC. The GC members were each asked to propose 10 symptoms/signs/tests that they felt would have the most potential to predict later diagnosis in people with suspected ME, and to email these lists to the technical team. The entire list was then analysed by 3 RFs separately, who each compiled lists of the top 5 tests and top 5 symptoms/signs based on the prevalence across the suggestions provided by the entire GC. Each RF produced similar but slightly different lists, based on different methods of categorisation and interpretation. Because every GC member used slightly different terminology to describe a test, symptom or sign, and because they also varied in how inclusive a term was, there was a certain amount of ambiguity in interpreting the information and organising the information into meaningful categories. Thus there were slight differences in endpoint

		between the 3 RFs. These were then combined, by including any that were in the top 5 in any of the 3 lists [using Boolean logic = (top 5 RF1) OR (top 5 RF2) OR (top 5 RF3)] which would mean > 5 in the final lists but allowed for the fact that the RFs used slightly different categorisation strategies and interpretation. Based on this strategy, final selected index tests were: • 2-day Cardiopulmonary exercise testing • grip strength • IMS • Cytokine profile • ESR • mitochondrial function tests • postural hypotension test • CRP Selected signs/symptoms are in separate protocol.
8.	Reference standard	Clinical diagnosis of ME/CFS
9.	Types of study to be included	Diagnostic randomised controlled trials (test and treat trials) Cross-sectional studies Exclusion: Studies where the index test informs the eventual diagnosis

		Case-control studies Rationale for exclusion of case-control studies: Case control studies (where participants with a diagnosis or no diagnosis are asked to recall previous status of tests/signs/symptoms measured or experienced prior to diagnosis) are regarded as too inaccurate and prone to recall bias to provide reliable results.
10.	Other exclusion criteria	Studies that do not report sensitivity and specificity, or insufficient data to derive these values. Non-English language studies.
11.	Context	N/A

12.	Primary outcomes (critical outcomes)	**Diagnostic RCT:**
		CRITICAL
		• Mortality
		• General symptom scales (any validated scales). For example:
		  ○ De Paul Symptom Questionnaire
		  ○ Self-Rated Clinical Global Impression Change Score
		• Fatigue/fatiguability (any validated scales). For example:
		  ○ Chalder fatigue Scale
		  ○ Fatigue Severity Scale
		  ○ Fatigue Impact scale
		• Physical functioning (any validated scales). For example:
		  ○ SF36 physical function
		  ○ SF36 PCS
		• Cognitive function (any validated scales). For example:

		○ MMSE • Psychological status (any validated scales). For example: ○ Hospital Anxiety and Depression Scale ○ 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 **Measures of diagnostic accuracy:** • Sensitivity • Specificity • Area under the curve

		• Likelihood ratios • Predictive values
13.	Secondary outcomes (important outcomes)	**Diagnostic RCT** **IMPORTANT OUTCOMES:** • Care needs • Impact on families and carers
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of these potentially eligible studies will be retrieved and assessed in line with the criteria outlined above. A standardised form will be used to extract data from the included studies (see Developing NICE guidelines: the manual section 6.4). Data extraction will be independently quality assured by a second reviewer, discrepancies will be identified and resolved through discussion (with a third party where necessary).
15.	Risk of bias (quality) assessment	Risk of bias quality assessment will be assessed using QUADAS-2.

		Assessment will be independently quality assured by a second reviewer. Disagreements between the reviewers will be resolved by discussion, with involvement of a third party where necessary.
16.	Strategy for data synthesis	Where possible data will be meta-analysed where appropriate (if at least 3 studies reporting data at the same diagnostic threshold) in WinBUGS. Summary diagnostic outcomes will be reported from the meta-analyses with their 95% confidence intervals in adapted GRADE tables. Heterogeneity will be assessed by visual inspection of the sensitivity and specificity plots and summary area under the curve (AUC) plots. Particular attention will be placed on specificity determined by the committee to be the primary outcome for decision making. If meta-analysis is not possible, data will be presented as individual values in adapted GRADE profile tables and plots of un-pooled sensitivity and specificity from RevMan software.
17.	Analysis of sub-groups	Stratification: Age: children / adults Subgroups to investigate if heterogeneity is present: None
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	02/01/2018		
22.	Anticipated completion date	22/08/2019		
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: [NICE guideline webpage].
29.	Other registration details	N/A
30.	Reference/URL for published protocol	

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. [Add in any additional agree dissemination plans.]
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

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2 **Review protocol: predictive accuracy of clinical signs and symptoms**

0.	PROSPERO registration number	
1.	Review title	What are the predictive accuracies of specific clinical symptoms/signs, to identify those who will subsequently be given a clinical diagnosis of ME/CFS?
2.	Review question	What are the predictive accuracies of specific clinical symptoms/signs, to identify those who will subsequently be given a clinical diagnosis of ME/CFS?
3.	Objective	To identify signs/symptoms that can help to predict who is more likely to go on to get a clinical diagnosis of 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 Searches will be restricted by:

		• English language Other searches: • None The searches may be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion if relevant. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	ME/CFS
6.	Population	Adults, children and young people who are suspected of having ME/CFS by their primary clinician.
7.	Intervention/Exposure/Test	A prioritised list of clinical signs/symptoms was decided by the GC. The GC members were each asked to propose 10 symptoms/signs/tests that they felt would have the most potential to predict later diagnosis in people with suspected ME, and to email these lists to the technical team. The entire list was then analysed by 3 RFs separately, who each compiled lists of the top 5 tests and top 5 symptoms/signs based on the prevalence across the suggestions provided by the entire GC. Each RF produced similar but slightly different lists, based on different methods of

		categorisation and interpretation. Because every GC member used slightly different terminology to describe a test, symptom or sign, and because they also varied in how inclusive a term was, there was a certain amount of ambiguity in interpreting the information and organising the information into meaningful categories. Thus there were slight differences in endpoint between the 3 RFs. These were then combined, by including any that were in the top 5 in any of the 3 lists [using Boolean logic = (top 5 RF1) OR (top 5 RF2) OR (top 5 RF3)] which would mean > 5 in the final lists but allowed for the fact that the RFs used slightly different categorisation strategies and interpretation. Based on this strategy, final selected symptoms/signs were: • Cognitive dysfunction • Post Exercise Malaise • Severe fatigue after minimal mental or physical effort • Sleep disorders • Sensitivity to sound or light • Gastrointestinal problems (such as nausea or IBS). Selected tests are in separate protocol.
8.	Reference standard	Clinical diagnosis of ME/CFS

9.	Types of study to be included	Prospective and retrospective longitudinal cohort studies, that evaluate the predictive accuracy of clinical signs/symptoms. Exclusion: Cross-sectional studies Case-control studies Rationale for exclusion of cross-sectional and case-control studies: Cross-sectional studies, where associations between ME status [diagnosed with ME or not diagnosed with ME] and index data [presence or absence of a positive symptom/sign] are evaluated at the same point in time, will involve a different population to the one in this question. We are looking only at the intended target population – people who suspected of having ME/CFS but are not yet diagnosed. In contrast, a cross-sectional study will look at a population that are already diagnosed. This distinction between populations is important because associations between index data and eventual diagnostic status may be different for measurements of index data made during the pre-diagnosis stage and measurements of index data made when the diagnosis is established. One reason for this is that index data may change during the time elapsing before eventual diagnosis, and therefore the strengths of association may also change. Only the strength of association derived from index data in people who are as yet undiagnosed is relevant because it is in these people that we need to make estimates of likely future diagnosis. It should be remembered that the purpose of this question is to allow clinicians to pick out the people who are most likely to

		get diagnosed so they can be prioritised for early pre-diagnosis management. Case control studies (where participants with a diagnosis or no diagnosis are asked to recall previous status of tests/signs/symptoms measured or experienced prior to diagnosis) are regarded as too inaccurate and prone to recall bias to provide reliable results.
10.	Other exclusion criteria	Studies that do not report sensitivity and specificity, or insufficient data to derive these values. Non-English language studies.
11.	Context	N/A
12.	Primary outcomes (critical outcomes)	• Sensitivity • Specificity • Area under the curve • Likelihood ratios • Predictive values
13.	Secondary outcomes (important outcomes)	N/A
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

		The full text of these potentially eligible studies will be retrieved and assessed in line with the criteria outlined above. A standardised form will be used to extract data from the included studies (see Developing NICE guidelines: the manual section 6.4). Data extraction will be independently quality assured by a second reviewer, discrepancies will be identified and resolved through discussion (with a third party where necessary).
15.	Risk of bias (quality) assessment	Risk of bias quality assessment will be assessed using QUADAS-2. Assessment will be independently quality assured by a second reviewer. Disagreements between the reviewers will be resolved by discussion, with involvement of a third party where necessary.
16.	Strategy for data synthesis	Where possible data will be meta-analysed where appropriate (if at least 3 studies reporting data at the same diagnostic threshold) in WinBUGS. Summary diagnostic outcomes will be reported from the meta-analyses with their 95% confidence intervals in adapted GRADE tables. Heterogeneity will be assessed by visual inspection of the sensitivity and specificity plots and summary area under the curve (AUC) plots. Particular attention will be placed on specificity determined by the committee to be the primary outcome for decision making. If meta-analysis is not possible, data will be presented as individual values in adapted GRADE profile tables and plots of un-pooled sensitivity and specificity from RevMan software.

17.	Analysis of sub-groups	Stratification: Age: children / adults Subgroups to investigate if heterogeneity is present: None		
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	02/01/2018		
22.	Anticipated completion date	22/08/2019		
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: [NICE guideline webpage].
29.	Other registration details	N/A
30.	Reference/URL for published protocol	
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. [Add in any additional agree dissemination plans.]
32.	Keywords	Diagnosis, hypertension, high blood pressure
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

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2 **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).[125] **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.

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Appendix B Literature search strategies

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

- In people with suspected ME/CFS, what are the criteria used to establish a diagnosis?
- What are the predictive accuracies of specific tests, or clinical symptoms/signs, to identify people who will subsequently be given a definitive diagnosis of ME/CFS?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[125]

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 9: 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

1 **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

1 **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)

1 **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

2 **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"))

3 **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.21 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 10: 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

1 **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

1 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

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Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of diagnostic criteria

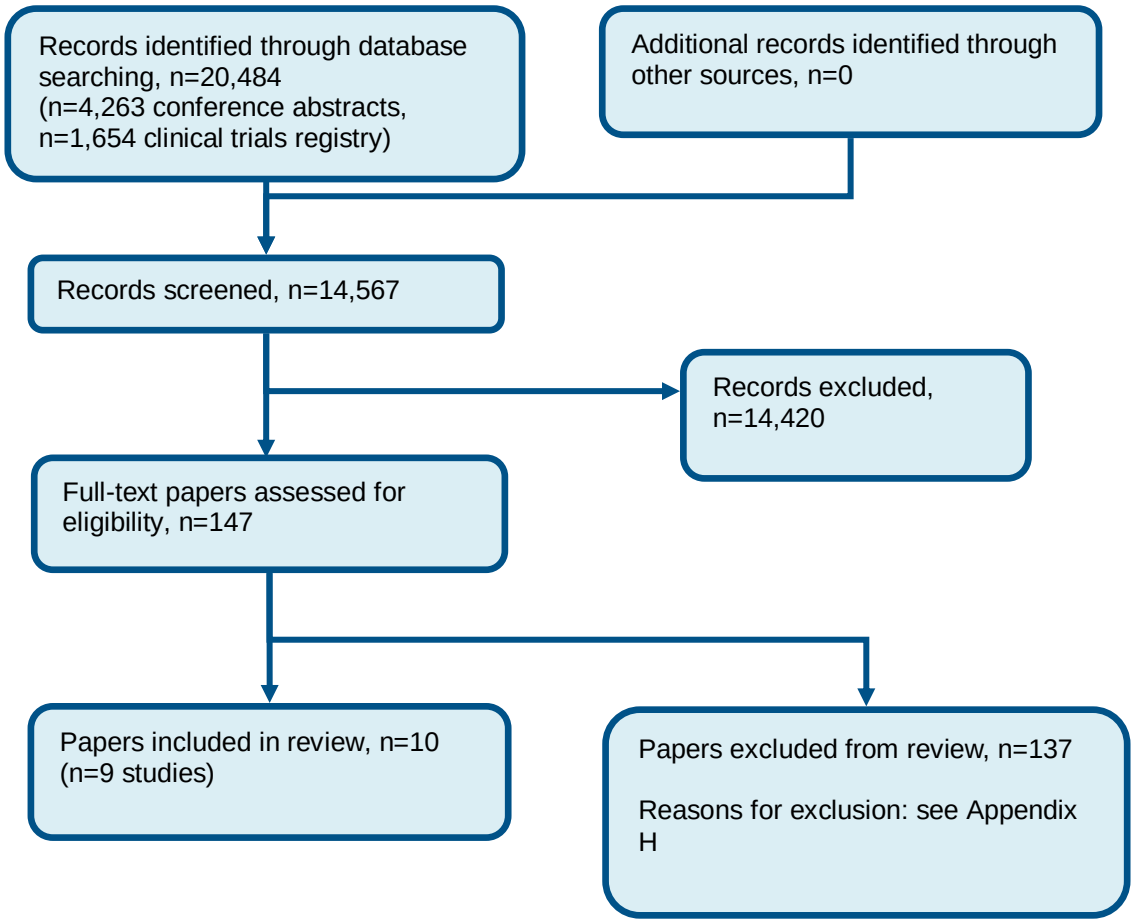


Figure 2: Flow chart of clinical study selection for the review of diagnostic test accuracy

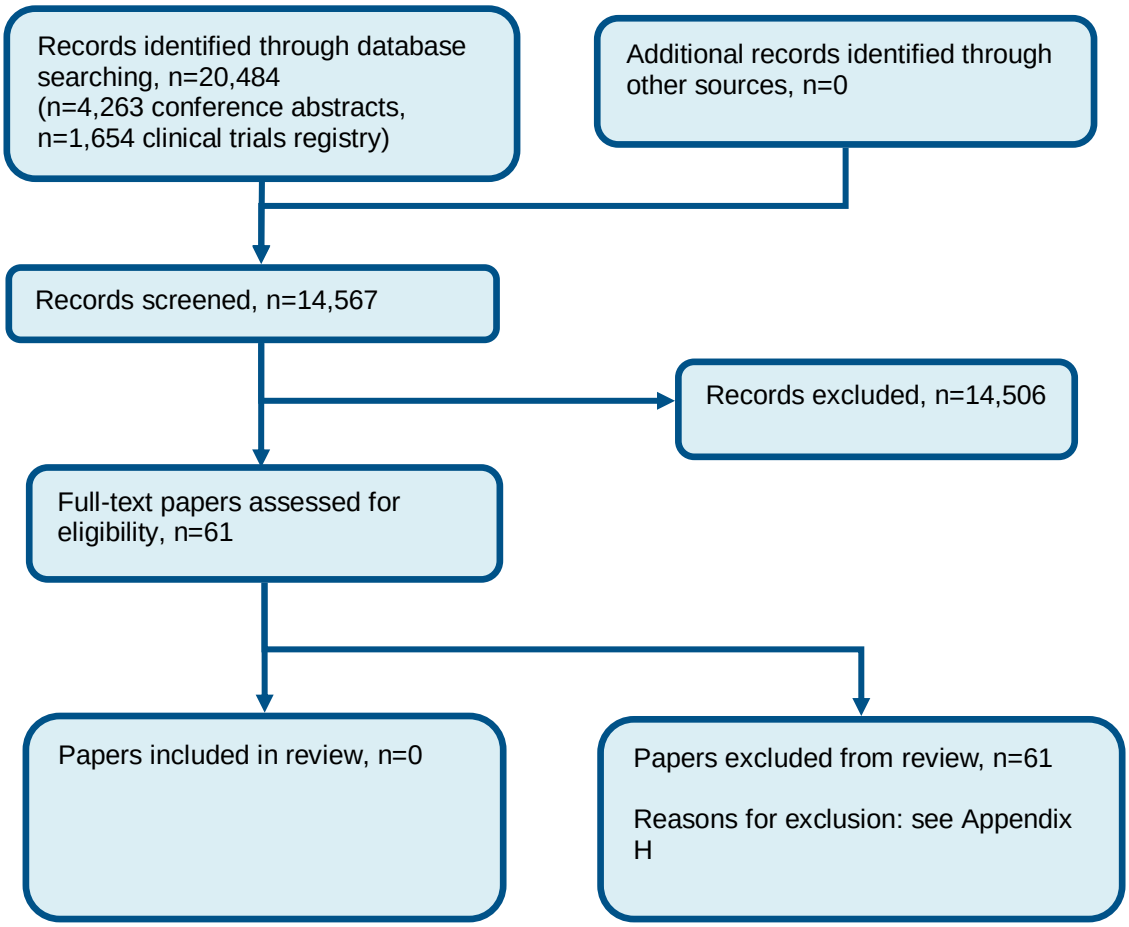
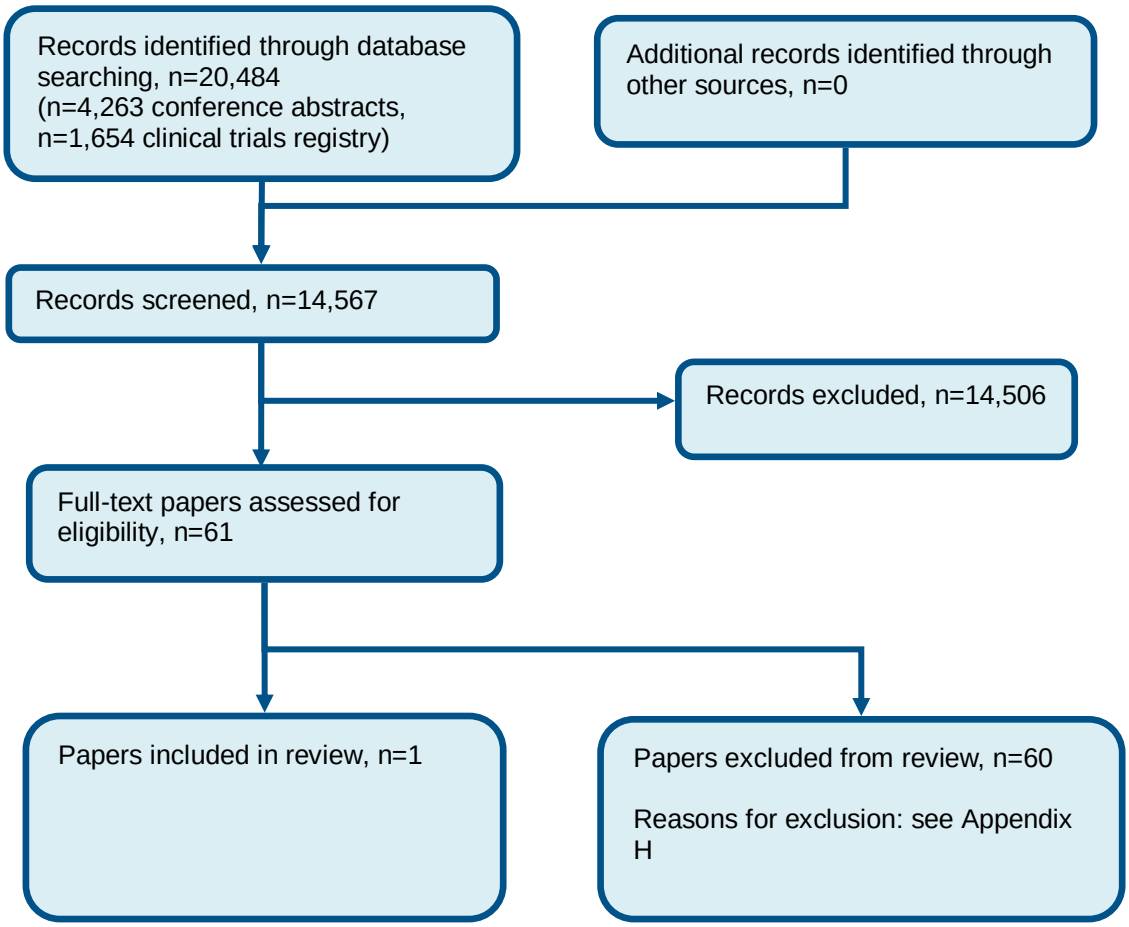


Figure 3: Flow chart of clinical study selection for the review of predictive accuracy of clinical signs and symptoms



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Appendix D – Diagnostic criteria: quality assessment of the criteria

The Appraisal of Guidelines for REsearch & Evaluation (AGREE) Instrument was developed to address the issue of variability in guideline quality. To that end, the AGREE instrument is a tool that assesses the methodological rigour and transparency in which a guideline is developed. The original AGREE instrument has been refined, which has resulted in the new AGREE II. AGREE II has six domains and an overall assessment. The domains are listed below:

- Domain 1**. Scope and Purpose** is concerned with the overall aim of the guideline, the specific health questions, and the target population
- Domain 2. **Stakeholder Involvement** focuses on the extent to which the guideline was developed by the appropriate stakeholders and represents the views of its intended users
- Domain 3. **Rigour of Development** relates to the process used to gather and synthesize the evidence, the methods to formulate the recommendations, and to update them
- Domain 4. **Clarity of Presentation** deals with the language, structure, and format of the guideline
- Domain 5. **Applicability** pertains to the likely barriers and facilitators to implementation, strategies to improve uptake, and resource implications of applying the guideline
- Domain 6. **Editorial Independence** is concerned with the formulation of recommendations not being unduly biased with competing interests
- Overall assessment includes the rating of the overall quality of the guideline and whether the guideline would be recommended for use in practice.

Although this review doesn't include guidelines the principles of the decision making are similar in developing consensus based diagnostic criteria and has been used the evaluation of consensus statements. While applying the AGREE II tool and assigning a score is less useful in this context the relevant items in the domains provide a robust set of principles to measure in the consensus criteria development. Table 10 sets out the AGREE II domains and the relevant items evaluated in this review.

Table 11: Critical appraisal criteria

AGREE II	Items used in the criteria assessment	Description
Domain 1**. Scope and Purpose**	Objectives ➢ Health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) ➢ Expected benefit(s) or outcome(s) ➢ Target(s) (e.g., patient population, society)	Report the overall objective(s) of the guideline. The expected health benefits from the guideline are to be specific to the clinical problem or health topic.
	Questions ➢ Target population ➢ Intervention(s) or exposure(s) ➢ Comparisons (if appropriate) ➢ Outcome(s) ➢ Health care setting or context	Report the health question(s) covered by the guideline, particularly for the key recommendations.
	Population ➢ Target population, sex and age ➢ Clinical condition (if relevant)	Describe the population (i.e., patients, public, etc.) to whom

AGREE II	Items used in the criteria assessment	Description
	➢ Severity/stage of disease (if relevant) ➢ Comorbidities (if relevant) ➢ Excluded populations (if relevant)	the guideline is meant to apply.
Domain 2. **Stakeholder Involvement**	Group membership ➢ Name of participant ➢ Discipline/content expertise (e.g., neurosurgeon, methodologist) ➢ Institution (e.g., St. Peter's hospital) ➢ Geographical location (e.g., Seattle, WA) ➢ A description of the member's role in the guideline development group	Report all individuals who were involved in the development process. This may include members of the steering group, the research team involved in selecting and reviewing/rating the evidence and individuals involved in formulating the final recommendations.
	Target population preferences and views ➢ Statement of type of strategy used to capture patients'/publics' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences) ➢ Methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups) ➢ Outcomes/information gathered on patient/public information ➢ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	Report how the views and preferences of the target population were sought/considered and what the resulting outcomes were.
	Target users ➢ The intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators) ➢ How the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care)	Report the target (or intended) users of the guideline.
Domain 3. **Rigour of Development**	Search methods ➢ Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL) ➢ Time periods searched (e.g., January 1, 2004 to March 31, 2008) ➢ Search terms used (e.g., text words, indexing terms, subheadings) ➢ Full search strategy included (e.g., possibly located in appendix)	Report details of the strategy used to search for evidence.
	Evidence selection criteria ➢ Target population (patient, public, etc.) characteristics ➢ Study design ➢ Comparisons (if relevant) ➢ Outcomes ➢ Language (if relevant)	Report the criteria used to select (i.e., include and exclude) the evidence. Provide rationale, where appropriate.

AGREE II	Items used in the criteria assessment	Description
	➢ Context (if relevant)	
	Strengths and limitations of the evidence ➢ Study design(s) included in body of evidence ➢ Study methodology limitations (sampling, blinding, allocation concealment, analytical methods) ➢ Appropriateness/relevance of primary and secondary outcomes considered ➢ Consistency of results across studies ➢ Direction of results across studies ➢ Magnitude of benefit versus magnitude of harm ➢ Applicability to practice context	Describe the strengths and limitations of the evidence. Consider from the perspective of the individual studies and the body of evidence aggregated across all the studies. Tools exist that can facilitate the reporting of this concept.
	Formulation of recommendations ➢ Recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered) ➢ Outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures) ➢ How the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations and the final vote)	Describe the methods used to formulate the recommendations and how final decisions were reached. Specify any areas of disagreement and the methods used to resolve them.
	Consideration of benefits and harms ➢ Supporting data and report of benefits ➢ Supporting data and report of harms/side effects/risks ➢ Reporting of the balance/trade-off between benefits and harms/side effects/risks ➢ Recommendations reflect considerations of both benefits and harms/side effects/risks	Report the health benefits, side effects, and risks that were considered when formulating the recommendations.
	Link between recommendations and evidence ➢ How the guideline development group linked and used the evidence to inform recommendations ➢ Link between each recommendation and key evidence (text description and/or reference list) ➢ Link between recommendations and evidence summaries and/or evidence tables in the results section of the guideline	Describe the explicit link between the recommendations and the evidence on which they are based.
	External review ➢ Purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations,	Report the methodology used to conduct the external review.

AGREE II	Items used in the criteria assessment	Description
	assess applicability and feasibility, disseminate evidence) ➢ Methods taken to undertake the external review (e.g., rating scale, open-ended questions) ➢ Description of the external reviewers (e.g., number, type of reviewers, affiliations) ➢ Outcomes/information gathered from the external review (e.g., summary of key findings) ➢ How the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations)	
	Updating procedure ➢ A statement that the guideline will be updated ➢ Explicit time interval or explicit criteria to guide decisions about when an update will occur ➢ Methodology for the updating procedure	Describe the procedure for updating the guideline.
Domain 4. **Clarity of Presentation**	Specific and unambiguous recommendations ➢ A statement of the recommended action ➢ Intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects) ➢ Relevant population (e.g., patients, public) ➢ Caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply) ➢ If there is uncertainty about the best care option(s), the uncertainty should be stated in the guideline	Describe which options are appropriate in which situations and in which population groups, as informed by the body of evidence.
	Management options ➢ Description of management options ➢ Population or clinical situation most appropriate to each option	Describe the different options for managing the condition or health issue.
	Identifiable key recommendations ➢ Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms ➢ Specific recommendations grouped together in one section	Present the key recommendations so that they are easy to identify.
Domain 5. **Applicability**	Facilitators and barriers to application ➢ Types of facilitators and barriers that were considered ➢ Methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key	Describe the facilitators and barriers to the guideline's application.

AGREE II	Items used in the criteria assessment	Description
	stakeholders, pilot testing of guidelines before widespread implementation) ➢ Information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography) ➢ How the information influenced the guideline development process and/or formation of the recommendations	
	Implementation advice/tools ➢ Additional materials to support the implementation of the guideline in practice. For example: • Guideline summary documents • Links to check lists, algorithms • Links to how-to manuals • Solutions linked to barrier analysis (see Item 18) • Tools to capitalize on guideline facilitators (see Item 18) • Outcome of pilot test and lessons learned	Provide advice and/or tools on how the recommendations can be applied in practice.
	Resource implications ➢ Types of cost information that were considered (e.g., economic evaluations, drug acquisition costs) ➢ Methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc.) ➢ Information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course) ➢ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	Describe any potential resource implications of applying the recommendations.
	Monitoring/auditing criteria ➢ Criteria to assess guideline implementation or adherence to recommendations ➢ Criteria for assessing impact of implementing the recommendations ➢ Advice on the frequency and interval of measurement ➢ Operational definitions of how the criteria should be measured	Provide monitoring and/or auditing criteria to measure the application of guideline recommendations.

AGREE II	Items used in the criteria assessment		Description
Domain 6. **Editorial Independence**	Funding body ➢ The name of the funding body or source of funding (or explicit statement of no funding) ➢ A statement that the funding body did not influence the content of the guideline		Report the funding body's influence on the content of the guideline.
	Competing interests ➢ Types of competing interests considered ➢ Methods by which potential competing interests were sought ➢ A description of the competing interests ➢ How the competing interests influenced the guideline process and development of recommendations		Provide an explicit statement that all group members have declared whether they have any competing interests.
Overall assessment	No serious limitations	All six domains met/ (four domains met and) two domains met partially/ (five domains met and) only one domain not met	
	Serious limitations	(Three domains met and) limitations across three domains with no more than two domains not met/ (four domains met and) limitations across two domains with no more than one domain not met	
	Very serious limitations	Three or more domains not met/ (two domains not met and) more than one domain met partially/ limitations across four or more domains	

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1 Appendix E – Effectiveness evidence

E2 1.1 Diagnostic criteria

Study	Quality domains						Overall rating [a]
	Scope and purpose	Stakeholder involvement	Rigour of development	Clarity of presentation	Applicability	Editorial independence	
Fukuda 1994[42]	Objectives and expected outcomes are clearly reported Target population and setting are clearly reported; intervention, comparator and outcomes are not applicable Population is partially described; clinical condition, comorbidities and exclusionary conditions are described but no mention of age or severity MET	Group membership is partially reported; names, institutions and geographical locations are reported, but discipline/content expertise and role in the group not reported No information reported on how the views and preferences of the target population were sought/considered, or what the outcomes were The intended users and use of the publication	No report of criteria being based on evidence from a systematic literature review Methods used to formulate criteria and reach final decisions not described Unclear link between evidence and criteria No external review reported No updating procedure described NOT MET	Clear criteria are presented and include caveats where relevant, but level of uncertainty is not reported Reporting of management options not applicable Criteria summarised in a flow chart and grouped by topic MET	Consideration of barriers and facilitators to application not reported No additional materials to support implementation Consideration of potential resource implications not reported Monitoring/auditing criteria not reported NOT MET	No statement about funding No statement about competing interests NOT MET	Very serious limitations

Study	Quality domains						Overall rating [a]
	Scope and purpose	**Stakeholder involvement**	**Rigour of development**	**Clarity of presentation**	**Applicability**	**Editorial independence**	
		are clearly reported PARTIAL					
Carruthers 2011[17,16]	Objectives and expected outcomes are clearly reported Target population and setting are clearly reported; intervention, comparator and outcomes are not applicable Population is clearly described MET	Group membership is partially reported; names, institutions, geographical locations and discipline/content expertise are reported, but role in the group not reported Consensus panel included a patient advocate, but unclear methods by which views/preferences were sought or how they were used to inform the criteria The intended users and use of the publication	Literature review included in the paper and brief discussion of inconsistency, but search strategy, evidence selection, quality assessment or how the findings were incorporated into the criteria not reported Method of agreeing criteria and consensus level clearly reported No external review reported No updating procedure described	Clear criteria are presented and include operational notes where relevant, but level of uncertainty is not reported Reporting of management options not applicable Criteria presented in a table and grouped by symptom type MET	Considerations for clinical and research application are reported, but unclear how these were derived Primer published to support implementation Consideration of potential resource implications not reported Monitoring/auditing criteria not reported PARTIAL	Statement that no funding was received Statement that no members had competing interests PARTIAL	Very serious limitations

Study	Quality domains						Overall rating [a]
	Scope and purpose	**Stakeholder involvement**	**Rigour of development**	**Clarity of presentation**	**Applicability**	**Editorial independence**	
		are clearly reported PARTIAL	PARTIAL				
Carruthers 2003[15]	Objectives and expected outcomes are clearly reported Target population and setting are clearly reported; intervention, comparator and outcomes are not applicable Population is partially described; clinical condition, comorbidities and exclusionary conditions are described but severity not clearly described MET	Group membership details not reported No information reported on how the views and preferences of the target population were sought/considered, or what the outcomes were The intended users and use of the publication are clearly reported PARTIAL	No report of criteria being based on evidence from a systematic literature review Methods used to formulate criteria and reach final decisions not clearly described Unclear link between evidence and criteria No external review reported No updating procedure described NOT MET	Clear criteria are presented and include operational notes where relevant, but level of uncertainty is not reported Reporting of management options not applicable Criteria presented in a box and grouped by symptom type MET	Considerations for clinical application are reported, but unclear how these were derived No additional materials to support implementation Consideration of potential resource implications not reported Monitoring/auditing criteria not reported NOT MET	No statement about funding No statement about competing interests NOT MET	Very serious limitations
Sharpe, 1991[147]	Objectives and expected	Group membership is	No report of criteria being	Criteria are presented,	Consideration of barriers and	Sources of funding reported	Very serious limitations

Study	Quality domains						Overall rating [a]
	Scope and purpose	**Stakeholder involvement**	**Rigour of development**	**Clarity of presentation**	**Applicability**	**Editorial independence**	
	outcomes are clearly reported Target population and setting are clearly reported; intervention, comparator and outcomes are not applicable Population is partially described; clinical condition and exclusionary conditions are described but no mention of age, severity or comorbidities MET	clearly reported; names, institutions, geographical locations, discipline/content expertise, role in the group No information reported on how the views and preferences of the target population were sought/considered, or what the outcomes were The intended users and use of the publication are clearly reported PARTIAL	based on evidence from a systematic literature review Methods used to formulate criteria and reach final decisions not clearly described Unclear link between evidence and criteria No external review reported No updating procedure described NOT MET	although some lack detail and level of uncertainty is not reported Reporting of management options not applicable Criteria are grouped by syndrome PARTIAL	facilitators to application not reported No additional materials to support implementation Consideration of potential resource implications not reported Monitoring/auditing criteria not reported NOT MET	including a pharmaceutical company and no statement that the funding body did not influence the publication No statement about competing interests NOT MET	
Institute of Medicine 2015[59]	Objectives and expected outcomes are clearly reported	Group membership is clearly reported; names, institutions, geographical	Clear reporting of the systematic literature review strategy; databases, time periods, search	Clear criteria are presented and include operational notes where relevant, but level of	Clear consideration of barriers and facilitators to application and methods by which	Sources of funding reported but no statement that the funding bodies did not	Serious limitations

Study	Quality domains						Overall rating [a]
	Scope and purpose	**Stakeholder involvement**	**Rigour of development**	**Clarity of presentation**	**Applicability**	**Editorial independence**	
	Target population and setting are clearly reported; intervention, comparator and outcomes are not applicable Population is clearly described MET	locations, discipline/content expertise, role in the group Clear reporting of how the views and preferences of the target population were sought/considered and what the outcomes were The intended users and use of the publication are clearly reported MET	terms, but full search strategy not included Evidence selection criteria are reported, although not in detail (no protocols presented) Strengths and limitations of the evidence appropriately considered using an adapted version of GRADE Methods used to formulate criteria are clearly described, although the outcomes of the development process (e.g. extent to which consensus was	uncertainty is not reported Reporting of management options not applicable Criteria presented in a box MET	information regarding them was sought Dissemination strategy included advice application in practice Consideration of potential resource implications not reported Recommendation for assessment of guideline implementation and impact, including definitions of how this should be measured PARTIAL	influence the publication No statement about competing interests PARTIAL	

Study	Quality domains						Overall rating [a]
	Scope and purpose	Stakeholder involvement	Rigour of development	Clarity of presentation	Applicability	Editorial independence	
			reached) was unclear Clear reporting of how the evidence was used to inform criteria, although no explicit link between individual recommendations and evidence Clear reporting of purpose and extent of external review and description of external reviewers, although unclear methods used and outcome of external review Recommendation for update of the criteria, including explicit time interval and methodology for				

Study	Quality domains						Overall rating [a]
	Scope and purpose	**Stakeholder involvement**	**Rigour of development**	**Clarity of presentation**	**Applicability**	**Editorial independence**	
			the updating procedure PARTIAL				
National Collaborating Centre for Primary Care, 2007[124]	Objectives and expected outcomes are clearly reported Target population and setting are clearly reported; intervention, comparator and outcomes are not applicable Population is clearly described MET	Group membership is partially reported; names, discipline/content expertise, role in the group, but institution and geographical location not reported Clear reporting of how the views and preferences of the target population were sought/considered and what the outcomes were The intended users and use of the publication are clearly reported MET	Clear reporting of the systematic literature review search strategy Evidence selection criteria are reported, although not in detail (no protocols presented) Strengths and limitations of the evidence not clearly reported Methods used to formulate criteria are clearly described.Clear reporting of how the evidence was used to inform criteria	Clear criteria are presented and level of uncertainty is reported (evidence quality in evidence statements) Reporting of management options not applicable Recommendations grouped by topic MET	Clear consideration of barriers and facilitators to application and methods by which information regarding them was sought Additional tools and resources developed to aid implementation Clear reporting of consideration of potential resource implications Monitoring/auditing criteria not reported PARTIAL	Source of funding reported but no statement that the funding bodies did not influence the publication No statement about competing interests NOT MET	Serious limitations

Study	Quality domains						Overall rating [a]
	Scope and purpose	**Stakeholder involvement**	**Rigour of development**	**Clarity of presentation**	**Applicability**	**Editorial independence**	
			Clear reporting of purpose and extent of external review, description of external reviewers, but unclear outcome of review and impact on the recommendations Clear reporting of the procedure for updating the guideline PARTIAL				
Holmes 1988[55]	Objectives and expected outcomes are clearly reported Target population and setting are clearly reported; intervention, comparator and outcomes are not applicable	Authors names, institution and geographical location reported, but discipline/content expertise and role in the group not reported and unclear whether the authors formed the development group	No report of criteria being based on evidence from a systematic literature review Methods used to formulate criteria and reach final decisions not clearly described	Criteria are clearly presented, although level of uncertainty is not reported Reporting of management options not applicable Criteria are grouped by	Consideration of barriers and facilitators to application not reported No additional materials to support implementation Consideration of potential resource	No statement about funding No statement about competing interests NOT MET	Very serious limitations

Study	Quality domains						Overall rating [a]
	Scope and purpose	**Stakeholder involvement**	**Rigour of development**	**Clarity of presentation**	**Applicability**	**Editorial independence**	
	Population is partially described; clinical condition and exclusionary conditions are described but no mention of age, severity or comorbidities MET	No information reported on how the views and preferences of the target population were sought/considered, or what the outcomes were The intended users and use of the publication are clearly reported PARTIAL	Unclear link between evidence and criteria No external review reported No updating procedure described NOT MET	major/minor/physical and numbered MET	implications not reported Monitoring/auditing criteria not reported NOT MET		
Jason 2006[66]	Objectives and expected outcomes are clearly reported Target population and setting are clearly reported; intervention, comparator and outcomes are not applicable	Authors names, discipline/content expertise, institution and geographical location reported, but role in the group not reported and unclear whether the authors formed the development group	Literature review included in the paper, but search strategy, evidence selection, quality assessment or how the findings were incorporated into the criteria not reported Methods used to formulate criteria	Clear criteria are presented and include operational notes where relevant, but level of uncertainty is not reported Reporting of management options not applicable	Consideration of barriers and facilitators to application not reported No additional materials to support implementation Consideration of potential resource	No statement about funding No statement about competing interests NOT MET	Very serious limitations

Study	Quality domains						Overall rating [a]
	Scope and purpose	**Stakeholder involvement**	**Rigour of development**	**Clarity of presentation**	**Applicability**	**Editorial independence**	
	Population is partially described; age, clinical condition, exclusionary conditions and comorbidities are described but no definition of severity MET	No information reported on how the views and preferences of the target population were sought/considered, or what the outcomes were The intended users and use of the publication are clearly reported PARTIAL	and reach final decisions not clearly described Partial link between evidence and criteria No external review reported No updating procedure described NOT MET	Criteria presented in a table, with categories of symptoms groups together MET	implications not reported Monitoring/auditing criteria not reported NOT MET		
Rowe 2017[140]	Objectives and expected outcomes are clearly reported Target population and setting are clearly reported; intervention, comparator and outcomes are not applicable	Group membership is partially reported; names, institution and geographical location, but discipline/content expertise and role in the group not reported No information reported on how the views and	No report of criteria being based on evidence from a systematic literature review Methods used to formulate criteria and reach final decisions not clearly described	Clear criteria are presented, but level of uncertainty is not reported Reporting of management options not applicable Criteria presented in a box and grouped	Consideration of barriers and facilitators to application not reported Additional materials to support implementation Consideration of potential resource	Source of funding reported and statement that funding body did not influence content No statement about competing interests PARTIAL	Very serious limitations

Study	Quality domains						Overall rating [a]
	Scope and purpose	**Stakeholder involvement**	**Rigour of development**	**Clarity of presentation**	**Applicability**	**Editorial independence**	
	Population is partially described; clinical condition, comorbidities and exclusionary conditions are described but severity not clearly described MET	preferences of the target population were sought/considered, or what the outcomes were The intended users and use of the publication are clearly reported PARTIAL	Unclear link between evidence and criteria No external review reported No updating procedure described NOT MET	according to symptoms MET	implications not reported Monitoring/auditing criteria not reported NOT MET		

(a) No serious limitations: all six domains met/ (four domains met and) two domains met partially/ (five domains met and) only one domain not met
Serious limitations: (three domains met and) limitations across three domains with no more than two domains not met/ (four domains met and) limitations across two domains with no more than one domain not met
Very serious limitations: three or more domains not met/ (two domains not met and) more than one domain met partially/ limitations across four or more domains.

E.1.2 Clinical signs and symptoms

Reference	**Jason 2011[82]**
Study type	Prospective cohort
Study methodology	Data source: structured psychiatric interview, medical history interview and complete medical examination of those screening positive for CFS-like illness Recruitment: stratified random sample of several neighbourhoods, specifically selected to contain individuals from different ethnic and socioeconomic profiles; one adult from each household was selected for screening of CFS-like illness
Number of patients	n = 108 (213 originally screened positive and were worked up at wave 1, but 105 were unable to be followed up at wave 2)

Reference	Jason 2011[82]
Patient characteristics	Age, mean (SD): CFS 40 (10.49) years, ICF 39.67 (16.5) years, exclusion 41.46 (10.49) years, controls 39.89 (12.2) years Gender (male to female ratio): 35:73 Ethnicity: Black (n=22), White (n=50), Hispanic/Latino (n=28), Other (n=8) Setting: ethnically and socioeconomically diverse city Country: USA Inclusion criteria: not reported (seems to be those from the original random community sample that screened positive on the *CFS Screening Questionnaire* at wave 1) Exclusion criteria: none reported. Exclusion criteria reported in the wave 1 study were being too ill to be interviewed or not speaking English/Spanish
Target condition	CFS
Index test(s) and reference standard	Index tests (clinical signs and symptoms) Other diagnoses (measured by structured psychiatric interview, medical history interview and complete medical examination, including the *Structured Clinical Interview for the DSM-IV* to assess current psychiatric diagnoses, and a modified version of *The Chronic Fatigue Questionnaire* to assess current and past medical history, fatigue severity, social role impairment, sleep disorders etc.): Muscle weakness Insomnia Hypersomnia Irritable Bowel Syndrome Fukuda symptoms (measured by structured psychiatric interview, medical history interview and complete medical examination, including the *Structured Clinical Interview for the DSM-IV* to assess current psychiatric diagnoses, and a modified version of *The Chronic Fatigue Questionnaire* to assess current and past medical history, fatigue severity, social role impairment, sleep disorders etc.): Unrefreshing sleep Impaired memory or concentration Post-exertional malaise Reference standard Final diagnosis of CFS.

Reference	Jason 2011[82]				
	Diagnosis was made by a team of physicians with access to all information gathered on each participant during each of the phases of the study. Two physicians independently rated each file and disagreements were resolved by a third reviewer according to: - the current U.S. definition of CFS - Idiopathic Chronic Fatigue (ICF) – those who had at least 6 months duration of fatigue, but with insufficient symptoms or fatigue to meet the case definition of CFS - exclusionary for CFS due to medically/psychiatrically explained chronic fatigue (refined Fukuda criteria as recommended by an International Research group and the CDC, e.g. morbid obesity is exclusionary as it could cause severe fatigue, but the Body Mass Index cut off has been changed to 40 or higher. In addition, a lifetime history of major depressive disorder with melancholic, anorexia nervosa, or bulimia is now not exclusionary if these conditions resolved more than 5 years before the onset of the current chronically fatiguing illness) – those who had medically explained chronic fatigue for at least 6 months duration of fatigue, but with medical explanations of the fatigue, and those with psychiatric explanations of the fatigue (e.g., delusional disorders, schizophrenia, etc.) - control - participants with no exclusionary illness and less than 6 months of fatigue. Time between measurement of index test and reference standard: 10 years				
2×2 table		Reference standard +	Reference standard −	Total	Note: One of the index tests listed in the review protocol is 'grip strength'. The study reported the % of people who had a diagnosis of 'muscle weakness', but it is unclear how this was measured.
	Muscle weakness +	17	48	65	
	Muscle weakness −	5	33	38	
	Total	22	81	103	
		Reference standard +	Reference standard −	Total	
	Insomnia +	12	37	49	
	Insomnia −	11	46	57	
	Total	23	83	106	
		Reference standard +	Reference standard -	Total	
	Hypersomnia+	7	32	39	
	Hypersomnia -	16	51	67	
	Total	23	83	106	

Reference	Jason 2011[82]				
		Reference standard +	Reference standard -	Total	
	IBS +	5	12	17	
	IBS -	18	71	89	
	Total	23	83	106	
		Reference standard +	Reference standard -	Total	
	Unrefreshing sleep +	20	56	76	
	Unrefreshing sleep -	3	25	28	
	Total	23	81	104	
		Reference standard +	Reference standard -	Total	
	Impaired memory or concentration+	19	48	67	
	Impaired memory or concentration-	4	34	38	
	Total	23	82	105	
		Reference standard +	Reference standard -	Total	Note: 50% of people in the CFS group and 50% in the exclusion group were positive for the PEM 'index test'. The numbers in this 2x2 table have been calculated based on the assumption of no missing data in these two groups.
	Post exertional malaise +	12	35	47	
	Post exertional malaise -	12	47	59	
	Total	24	82	106	

Reference	Jason 2011[82]
Statistical measures	Index text: muscle weakness Sensitivity 0.77 Specificity 0.41 Index test: insomnia Sensitivity 0.52 Specificity 0.55 Index text: hypersomnia Sensitivity 0.30 Specificity 0.61 Index text: IBS Sensitivity 0.22 Specificity 0.86 Index text: unrefreshing sleep Sensitivity 0.87 Specificity 0.31 Index text: impaired memory or concentration Sensitivity 0.83 Specificity 0.41 Index text: post-exertional malaise Sensitivity 0.50 Specificity 0.57
Source of funding	National Institute of Allergy and Infectious Diseases
Limitations	Risk of bias: patient selection, reference standard, flow and timing Indirectness: no indirectness
Comments	Numbers of index test positive and negative cases have been calculated from percentages reported. Some missing data have been assumed as percentages reported do not yield whole numbers.

Appendix F – Forest plots

F.1 Clinical signs and symptoms

Figure 4: Sensitivity and specificity of muscle weakness for predicting diagnosis of ME/CFS

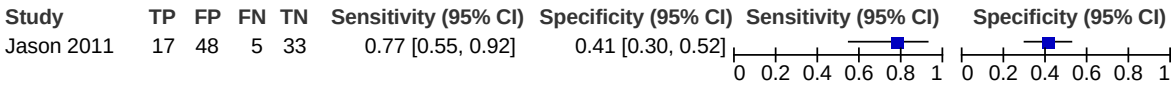


Figure 5: Sensitivity and specificity of insomnia for predicting diagnosis of ME/CFS

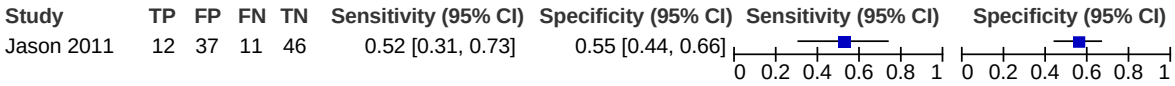


Figure 6: Sensitivity and specificity of hypersomnia for predicting diagnosis of ME/CFS

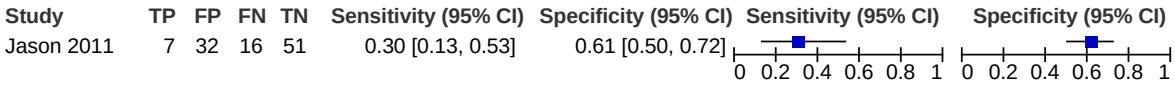


Figure 7: Sensitivity and specificity of IBS for predicting diagnosis of ME/CFS

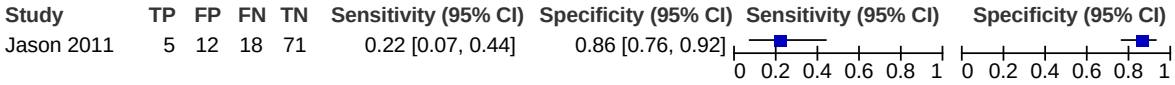


Figure 8: Sensitivity and specificity of unrefreshing sleep for predicting diagnosis of ME/CFS

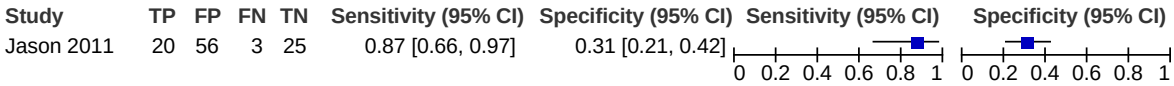


Figure 9: Sensitivity and specificity of impaired memory or concentration for predicting diagnosis of ME/CFS

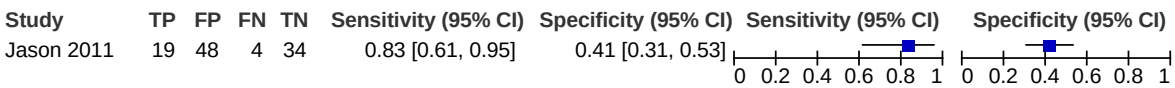
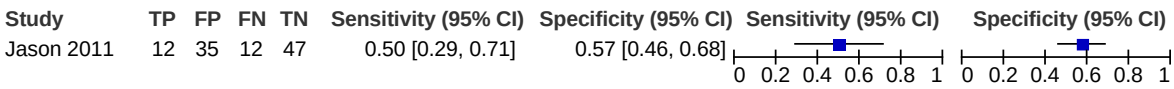
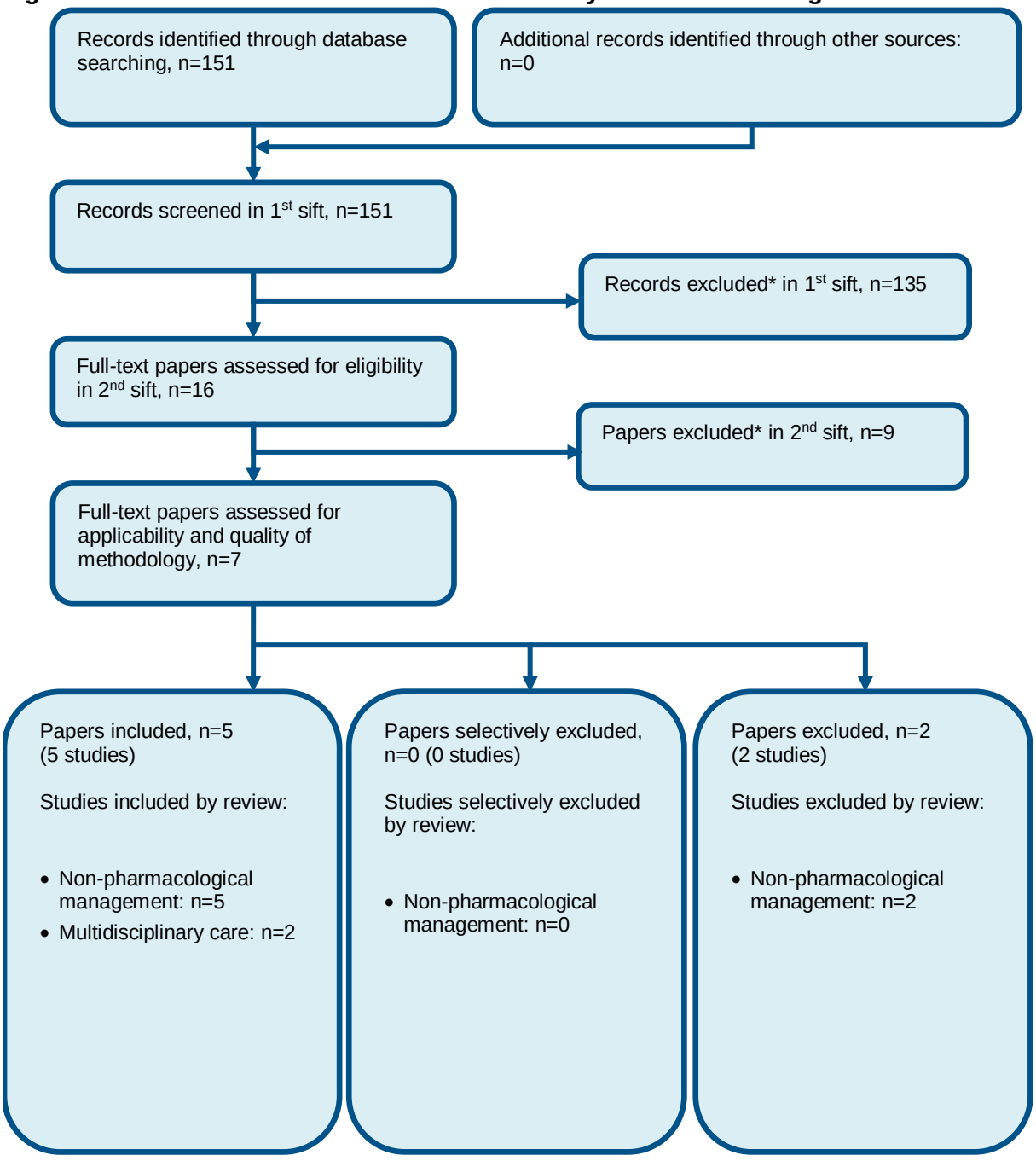


Figure 10: Sensitivity and specificity of post-exertional malaise for predicting diagnosis of ME/CFS



Appendix G – Economic evidence study selection

Figure 11: 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 – Excluded studies

Clinical studies

Table 12: Studies excluded from the diagnostic criteria clinical review

Reference	Reason for exclusion
Anonymous 1956[2]	Not original publication
Asprusten 2015[3]	not original publication; validation study
Asprusten 2018[5]	not original publication
Baraniuk 2017[6]	not original publication
Bates 1994[7]	not original publication
Bested 2015[8]	not original publication
Brimacombe 2002[9]	not original publication
Brown 2013[11]	not original publication
Brurberg 2014[12]	systematic review with different objective
Bruun Wyller 2006[13]	English language summary, full text in Norwegian; no criteria described
Carruthers 2007[14]	not original publication
Cassidy 1994[18]	not CFS; population does not match protocol
Chaudhuri, 2006[19]	not original publication
Christley 2012[20]	not original publication
Chu 2017[21]	not original publication
Clayton 2015[22]	brief overview of original report; complete report referenced & ordered
Cleare 2015[23]	not original publication
Coghlan 2015[24]	not original publication
Collin 2018[25]	not original publication
Craig 2002[26]	not original publication
Davenport 2014[27]	not original publication of criteria
Davenport 2011[28]	not original publication of criteria
De Becker 2001[29]	not original publication
De Silva 2013[31]	not original publication
de Vega 2018[32]	a study using DNA methylation profiles and health questionnaire scores to identify different ME/CFS subtypes
Deshpande 2015[33]	not original publication
Dowsett 1990[34]	criteria not based on consensus/guidelines
Eriksen 2018[36]	Not original publication
Estevez-Lopez 2018[37]	not original publication
Ferre 2018[39]	article not in English
Fukuda 1995[41]	duplicate
Fukuda 2008[43]	fatigue assessment scale, not original publication of criteria
Ganiats 2015[44]	not original publication
Glover 1995[45]	not original publication
Goudsmit 2009[46]	criteria not based on consensus/guidelines
Hartz 1998[47]	not original publication of criteria
Hawk Hines 2006[49]	not descriptive of any particular diagnostic criteria for ME/CFS
Helland 2017[50]	citation only
Hilgers 1996[52]	not descriptive of any particular diagnostic criteria for ME/CFS

Reference	Reason for exclusion
Ho-Yen 1990[54]	criteria not based on consensus/guidelines
Hyde 2007[58]	Criteria not based on consensus/guidelines.
Janal 2006[60]	not descriptive of any particular diagnostic criteria for ME/CFS
Jason 2009[63]	not original paper; references checked
Jason 2010[64]	not original paper; references checked
Jason 2012[65]	not original paper; references checked
Jason 2012[67]	not original publication
Jason 2013[68]	not original publication
Jason 2010[70]	not original publication
Jason 2015[71]	not original publication
Jason 2003[72]	not original publication
Jason 2014[74]	not original publication
Jason 2016[75]	not original publication
Jason 2015[76]	not original publication
Jason 2017[77]	not original paper; references checked
Jason 2017[78]	not original paper; references checked
Jason 2009[79]	not original publication
Jason 2010[81]	not original publication
Jason 2012[83]	not original paper; references checked
Jason 2015[84]	not original paper; references checked
Jason 2015[85]	not original paper; references checked
Jason 2016[86]	not original publication
Jason, 2014[87]	not original publication
Jason 2015[88]	not original publication
Jason 2015[89]	not original publication
Jason 2015[90]	not original publication
Jason 2015[91]	not original publication
Jason 2004[92]	not original publication
Jason 2001[93]	not original publication
Jason 2007[69]	propose a theoretically driven questionnaire relevant to particular symptoms-as a new case definition, testing its effectiveness in the diagnosis of CFS patients
Jason 2012[61]	Not based on consensus/guidelines
Jason 2010[62]	Not based on consensus/ guidelines
Jason 2015[73]	not original publication of established criteria
Johnston 2013[95]	citation only
Johnston 2013[94]	citation only
Johnston 2013[96]	systematic review with different objective
Johnston 2013[97]	not original publication
Johnston 2014[98]	not original publication
Johnston 2014[100]	not original publication
Johnston 2015[99]	citation only
Jones 2007[101]	criteria for post immunisation fatigue
Kennedy 2004[108]	not original publication
Komaroff 1991[110]	no diagnostic criteria described
Komaroff 1996[111]	Criteria not based on consensus/guidelines

Reference	Reason for exclusion
Lloyd 1988[114]	Unclear methodology for developed criteria
Lloyd 1990[113]	Not original publication
Maes 2012[116]	not original publication
Maes 2013[115]	not original publication
Meeus 2016[118]	not original publication
Morris 2013[120]	not original publication
Morris 2013[121]	duplicate
Nacul 2017[122]	not original publication
Osoba 2008[126]	Not based on consensus/guidelines
Prins 2006[129]	not original publication
Ramsay 1981[131]	no diagnostic criteria described
Reeves 2003[132]	not original publication
Reeves 2005[133]	criteria not based on consensus/guidelines
Revelas 2013[134]	not original publication
Rodriguez 2000[136]	not original publication
Ross 1996[139]	not original publication
Royal College of Paediatrics and Child Health, 2004[141]	not original publication
Schluedeberg 1992[143]	not original publication
Shi-Fu 1998[148]	not CFS; population does not match protocol
Shor 2003[149]	not original publication
Skapinakis, 2003[151]	not original publication
Song, 2005[156]	not original publication
Spracklen 1988[157]	not original publication
Stark 1999[158]	not original publication
Stough 2000[159]	not original publication
Stouten 2005[160]	not original publication
Strand 2016[161]	Not original publication
Strassheim 2018[162]	not original publication
Sullivan 2005[164]	not original publication
Sunnquist, 2015[165]	not original publication
Sunnquist 2017[166]	not original publication
Tan 2002[167]	not original publication
Tavris 1991[168]	not original publication
Taylor 1998[169]	not original publication
Tierney 1989[175]	not original publication
Tofoli 2011[176]	systematic review with different PICO
Toulkidis 2002[178]	not original publication
Twisk 2018[181]	not original publication
Twisk 2018[180]	definition not based on consensus/guidelines
Twisk 2018[179]	not original publication
Twisk 2014[184]	not original publication
Twisk 2015[182]	Critique of IOM, 2015
Twisk 2016[183]	not original publication
Twisk 2018[185]	not original publication

Reference	Reason for exclusion
Unger 2016[186]	not original publication
Vallings 2000[188]	not original publication
Vermeulen 2006[192]	not original publication
Wagner 2005[194]	not original publication
Wang 2014[196]	not diagnostic criteria
Williams 2014[203]	not original publication
Wyller 2013[204]	not original publication
Yancey 2012[205]	not original publication
Yiu 2006[206]	not original publication
Zala 1989[208]	not original publication

1

2 **Table 13: Studies excluded from the diagnostic tests clinical review**

Reference	Diagnostic test accuracy
Almenar-Perez 2020[1]	Incorrect population (diagnosed ME/CFS vs healthy controls); no relevant tests
Asprusten 2019[4]	No relevant tests; incorrect population (EBV infection at baseline but no suspicion of ME/CFS); ME/CFS diagnosis at follow up not reported
Davenport, 2014[27]	Conference abstract
De Meirleir 2018[30]	Incorrect population (diagnosed ME vs healthy controls)
Eguchi 2020[35]	Incorrect population (diagnosed ME/CFS vs healthy controls)
Eyskens 2019[38]	Incorrect population (only patients with confirmed CFS were included)
Fujii 2020[40]	Incorrect population (all participants had diagnosed ME/CFS) and no relevant tests
Harvey 2016[48]	No relevant tests
Hempel 2008[51]	Systematic review with incorrect PICO (references screened)
Hives 2017[53]	Incorrect population ('CFS/ME' vs healthy controls); no relevant tests
Houdenhove 2009[190]	Literature review on aetiopathogenesis of ME/CFS; no relevant tests (references checked)
Huibers 2004[57]	No reference standard (no clinical diagnosis of ME/CFS; participants defined as CFS-like cases based on meeting research criteria); no relevant tests
Huibers 2004[56]	No reference standard (no clinical diagnosis of ME/CFS; participants defined as CFS-like cases based on meeting research criteria); no relevant tests
Jason 2009[80]	Literature review of epidemiological studies (references checked)
Jason 2011[82]	No relevant tests
Katz 2018[102]	Summary paper for 9 cohort studies (original papers of included studies checked)
Katz 2010[103]	Conference abstract
Katz 2013[104]	Incorrect population (CFS vs recovered controls post-infectious mononucleosis)
Katz 2009[105]	No relevant tests
Katz 2011[106]	Incorrect population (CFS vs recovered controls post-infectious mononucleosis); no relevant tests
Katz 2012[107]	Incorrect population (CFS vs recovered controls post-infectious mononucleosis)

Reference	Diagnostic test accuracy
Kerr 2002[109]	Incorrect population (B19 infection, not suspected ME/CFS)
Kristiansen 2019[112]	No useable outcome data
Magnus 2015[117]	Incorrect study design and population (epidemiological study of incidence of ME/CFS after influenza vaccine and/or infection in general population); no relevant outcomes
Monden 2020[119]	No relevant tests
Nacul 2018[123]	Incorrect population (participants with clinician diagnosed ME/CFS meeting study criteria for ME/CFS [CDC or Canadian criteria] compared to participants with clinician diagnosed ME/CFS not meeting study criteria, or healthy controls); no useable outcome data (continuous data)
Pedersen 2019[127]	Incorrect population (EBV infection at baseline, not suspected of having ME/CFS vs healthy controls)
Pedersen 2019[128]	Incorrect population (index test measured at baseline in people with acute EBV infection; not suspected of having ME/CFS)
Rajeevan 2018[130]	No useable outcome data (continuous data)
Rimes 2007[135]	Incorrect population (fatigue outcomes assessed in a general population not suspected of ME/CFS); no relevant tests
Roerink 2017[137]	No useable outcome data (results for relevant test not reported)
Roerink 2016[138]	Conference abstract
Russell 2019[142]	Incorrect population (observational study in people with hepatitis C undergoing IFN-alpha treatment)
Schmaling, 2005[144]	No relevant outcomes (predictors of clinical outcomes in people with ICF and CFS at baseline)
Schmaling, 2003[145]	No relevant outcomes (predictors of clinical outcomes in people with ICF and CFS at baseline)
Sharpe 1993[146]	No relevant tests
Skapinakis 2003[150]	No relevant tests; no reference standard (unexplained fatigue syndromes; ME/CFS status not reported)
Slomko 2019[152]	Incorrect population (all participants had confirmed ME/CFS at baseline)
Smith 2008[153]	No relevant tests
Smith 2003[154]	No relevant tests
Solomon 2004[155]	Incorrect population (all participants had confirmed ME/CFS at baseline)
Strand 2016[161]	No relevant tests
Strickland 2001[163]	No relevant tests
Taylor 2002[170]	No relevant tests
Tomas 2018[177]	Descriptive study (references checked)
Valdini 1989[187]	No reference standard (ME/CFS status not reported)
Van Campen 2020[189]	Incorrect population (all participants had diagnosed ME/CFS at baseline)
Van Mens-Verhulst 1998[191]	No reference standard (chronic fatigue vs non-chronic fatigue; ME/CFS status not reported); no relevant tests
Vollmer-Conna 2006[193]	No reference standard and no relevant outcomes (principal components and latent class analyses of people with medically unexplained fatigue; ME/CFS status not reported)
Wagner 1997[195]	No relevant tests; no reference standard (ME/CFS status not reported)
Wang 2017[197]	Systematic review; no relevant tests (references checked)

Reference	Diagnostic test accuracy
Wessely 1996[199]	No relevant tests
Wessely 1997[198]	No relevant tests
White 2001[201]	No relevant tests
White 1995[200]	No reference standard (no diagnosis of ME/CFS)
Whiteley 2004[202]	Incorrect reference standard (diagnosis of fibromyalgia and post-viral fatigue grouped with CFS)
Wolbeek 2008[171]	No reference standard (ME/CFS status not reported)
Wolbeek 2011[172]	No reference standard (severity of CFS-related symptoms, not diagnosis of ME/CFS)
Wolbeek 2007[173]	Incorrect population (not suspected of ME/CFS; already diagnosed as CFS or non-CFS fatigue at baseline)
Wolbeek 2008[174]	Incorrect population (unspecified fatigue vs healthy controls); no relevant tests
Young 2003[207]	Incorrect population (fatiguing syndromes in Gulf War veterans; not all suspected of having ME/CFS)

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2 **Table 14: Studies excluded from the signs/symptoms clinical review**

Reference	Signs/symptoms predictive accuracy
Almenar-Perez 2020[1]	Incorrect study design and population (cross-sectional study of ME/CFS vs healthy controls); no relevant signs/symptoms
Asprusten 2019[4]	No relevant signs/symptoms (physicians' intuition for predicting chronic fatigue); incorrect population (EBV infection at baseline but no suspicion of ME/CFS); ME/CFS diagnosis at follow up not reported
Davenport, 2014[27]	Conference abstract
De Meirleir 2018[30]	Incorrect study design and population (cross-sectional study of diagnosed ME vs healthy controls); no relevant signs/symptoms
Eguchi 2020[35]	Incorrect study design and population (cross-sectional study of diagnosed ME/CFS vs healthy controls); no relevant signs/symptoms
Eyskens 2019[38]	Incorrect population (only patients with confirmed CFS were included)
Fujii 2020[40]	Incorrect study design and population (cross-sectional; all participants had diagnosed ME/CFS) and no relevant tests
Harvey 2016[48]	No relevant signs/symptoms
Hempel 2008[51]	Systematic review with incorrect PICO (references screened)
Hives 2017[53]	Incorrect study design and population (cross-sectional case-control study comparing diagnosed 'CFS/ME' vs healthy controls); no relevant signs/symptoms
Houdenhove 2009[190]	Literature review on aetiopathogenesis of ME/CFS; no relevant signs/symptoms (references checked)
Huibers 2004[57]	No reference standard (no clinical diagnosis of ME/CFS; participants defined as CFS-like cases based on meeting research criteria)
Huibers 2004[56]	No reference standard (no clinical diagnosis of ME/CFS; participants defined as CFS-like cases based on meeting research criteria)
Jason 2009[80]	Literature review of epidemiological studies (references checked)
Katz 2018[102]	Summary paper for 9 cohort studies (original papers of included studies checked)
Katz 2010[103]	Conference abstract
Katz 2013[104]	Incorrect population (CFS vs recovered controls post-infectious mononucleosis); no useable outcome data reported

Reference	Signs/symptoms predictive accuracy
Katz 2009[105]	No relevant signs/symptoms
Katz 2011[106]	Incorrect population (CFS vs recovered controls post-infectious mononucleosis); no relevant signs/symptoms
Katz 2012[107]	Incorrect study design and population (cross-sectional study of CFS vs recovered controls post-infectious mononucleosis)
Kerr 2002[109]	Incorrect study design and population (cross-sectional of people with B19 infection, not suspected ME/CFS)
Kristiansen 2019[112]	Incorrect study design (cross-sectional) and no useable outcome data
Magnus 2015[117]	Incorrect study design and population (epidemiological study of incidence of ME/CFS after influenza vaccine and/or infection in general population); no relevant outcomes
Monden 2020[119]	Incorrect population (general population; participants who reported key symptoms of CFS at baseline were excluded so symptoms measured when ME/CFS not suspected)
Nacul 2018[123]	Incorrect population and study design (cross-sectional study; participants with clinician diagnosed ME/CFS meeting study criteria for ME/CFS [CDC or Canadian criteria] compared to participants with clinician diagnosed ME/CFS not meeting study criteria, or healthy controls); no relevant signs/symptoms
Pedersen 2019[127]	Incorrect population (EBV infection at baseline, not suspected of having ME/CFS vs healthy controls)
Pedersen 2019[128]	Incorrect population (signs/symptoms measured in people with acute EBV infection at baseline; not suspected of having ME/CFS)
Rajeevan 2018[130]	Incorrect study design (cross-sectional)
Rimes 2007[135]	Incorrect population (fatigue outcomes assessed in a general population not suspected of ME/CFS); no relevant signs/symptoms
Roerink 2017[137]	Incorrect study design (cross-sectional); no relevant signs/symptoms
Roerink 2016[138]	Conference abstract
Russell 2019[142]	Incorrect population (observational study in people with hepatitis C undergoing IFN-alpha treatment)
Schmaling, 2005[144]	No relevant outcomes (predictors of clinical outcomes in people with ICF and CFS at baseline)
Schmaling, 2003[145]	No relevant outcomes (predictors of clinical outcomes in people with ICF and CFS at baseline)
Sharpe 1993[146]	Incorrect study design (cross-sectional); no relevant signs/symptoms
Skapinakis 2003[150]	No relevant signs/symptoms; no reference standard (unexplained fatigue syndromes; ME/CFS status not reported)
Slomko 2019[152]	Incorrect population (all participants had confirmed ME/CFS at baseline)
Smith 2008[153]	Incorrect study design (cross-sectional); no relevant signs/symptoms
Smith 2003[154]	Incorrect study design (cross-sectional); no relevant signs/symptoms
Solomon 2004[155]	Incorrect population (all participants had confirmed ME/CFS at baseline)
Strand 2016[161]	Incorrect study design (cross-sectional); no relevant signs/symptoms
Strickland 2001[163]	Incorrect study design (cross-sectional)
Taylor 2002[170]	Incorrect population (predictors of continued chronic fatigue status in a population with chronic fatigue or CFS at baseline)
Tomas 2018[177]	Descriptive study (references checked)
Valdini 1989[187]	No reference standard (ME/CFS status not reported)

Reference	Signs/symptoms predictive accuracy
Van Campen 2020[189]	Incorrect study design and population (cross-sectional study of people with ME/CFS at baseline)
Van Mens-Verhulst 1998[191]	No reference standard and incorrect study design (cross-sectional study of chronic fatigue vs non-chronic fatigue; ME/CFS status not reported); no relevant signs/symptoms
Vollmer-Conna 2006[193]	Incorrect study design (cross-sectional); no reference standard and no relevant outcomes (principal components and latent class analyses of people with medically unexplained fatigue; ME/CFS status not reported)
Wagner 1997[195]	No relevant signs/symptoms; no reference standard (ME/CFS status not reported)
Wang 2017[197]	Systematic review of cross-sectional/case-control studies; no relevant signs/symptoms (references checked)
Wessely 1996[199]	Incorrect study design (cross-sectional)
Wessely 1997[198]	Incorrect study design (cross-sectional); no relevant signs/symptoms
White 2001[201]	Incorrect population (people with viral infection at baseline; not suspected of having ME/CFS); no relevant signs/symptoms
White 1995[200]	Incorrect population (people with viral infection at baseline; not suspected of having ME/CFS); no reference standard (no diagnosis of ME/CFS)
Whiteley 2004[202]	Incorrect study design and reference standard (cross-sectional study; diagnosis of fibromyalgia and post-viral fatigue grouped with CFS)
Wolbeek 2008[171]	No reference standard (ME/CFS status not reported) and incorrect study design (cross-sectional)
Wolbeek 2011[172]	No reference standard (severity of CFS-related symptoms, not diagnosis of ME/CFS)
Wolbeek 2007[173]	Incorrect study design and population (cross-sectional study of people not suspected of ME/CFS; already diagnosed as CFS or non-CFS fatigue at baseline)
Wolbeek 2008[174]	Incorrect population (unspecified fatigue vs healthy controls); no relevant signs/symptoms
Young 2003[207]	Incorrect population (fatiguing syndromes in Gulf War veterans; not all suspected of having ME/CFS)

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2004 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.

None.

Appendix I – Research recommendations

I.1.1 Research recommendation

What diagnostic tests are clinically and cost effective in people with suspected ME/CFS?

I.1.2 Why this is important

Currently there is no diagnostic test or pattern of tests for ME/CFS and it is recognised on clinical grounds alone. People with ME/CFS report delays in diagnosis and it is important to identify people with ME/CFS as early as possible to ensure they are given information to try to prevent worsening of symptoms and any further deterioration of health. Research has highlighted that many healthcare professionals lack the confidence and knowledge to recognise and diagnose ME/CFS and can find it difficult to distinguish from other conditions. Accurate diagnostic tests that correctly identify ME/CFS will support healthcare professionals to identify people who have ME/CFS and rule out those who do not. Based on their clinical experience the committee identified the following tests as potentially promising in the diagnosis of ME/CFS:

- 2-day cardiopulmonary exercise testing
- repeat grip strength
- cytokine profile
- ESR
- mitochondrial function tests
- postural hypotension test
- CRP

No studies were identified in the review on the diagnostic accuracy of any of those tests to inform recommendations in the area of identification and diagnosis of ME/CFS. There is therefore a need for high quality trials into the clinical and cost effectiveness of diagnostic tests for ME/CFS that will facilitate early diagnosis and potentially lead to better outcomes for people with ME/CFS.

I.1.3 Rationale for research recommendation / modified PICO

PICO question	Population: Adults, children and young people who are suspected of having ME/CFS by their GP/primary clinician using the NICE 2020 criteria Index tests(s): Key index tests • 1 and 2-day cardiopulmonary exercise testing • repeat grip strength • EBV serology • cytokine profile • mitochondrial function tests • postural hypotension test • inflammatory markers (C- reactive protein (CRP), Erythrocyte sedimentation rate (ESR) Reference standard: Clinical diagnosis Outcome(s): sensitivity and specificity

Importance to patients or the population	At present there are no diagnostic tests or pattern of tests for ME/CFS. This leads to delays in diagnosis and misdiagnosis, resulting in people not receiving appropriate and/or timely care for ME/CFS or a differential diagnosis. A diagnostic test, the accuracy of which is established in a clinical trial, can lead to quicker access to care and better outcomes for people with ME/CFS either by ruling in or out the condition.
Relevance to NICE guidance	Good quality research in this area will address the lack of existing evidence to guide the diagnosis of ME/CFS and inform the development of future recommendations on a diagnostic test for the accurate detection of ME/CFS.
Relevance to the NHS	Recommendations for diagnostic tests for ME/CFS can offer clinicians clearer guidance on how to diagnose ME/CFS and are likely to overcome diagnostic delay leading to appropriate care and better outcomes for people with ME/CFS.
National priorities	None
Current evidence base	No studies were identified for this review.
Equality	The recommendation is unlikely to impact on equality issues.
Study design	Cross-sectional diagnostic study. Ideally all index tests would be evaluated on each participant.
Feasibility	The proposed research can be carried out on a realistic timescale and at a reasonable cost. This area of research is likely to be of high interest to people with ME/CFS due to the delay to diagnosis that many have experienced. This should ensure the identification an adequate sample size to enable the study. Identification of a sample could be through GP surgeries and patient support charities. The absence of an established reference standard for the diagnosis of ME/CFS can be challenging; however, clinical diagnosis based on the 'NICE 2020 criteria' that have been informed by a review of all existing peer-reviewed diagnostic criteria and clinical expertise is likely to overcome this.
Other comments	none
Importance	High: the research is of interest and will fill existing evidence gaps.

I.1.4 Research recommendation

In people with suspected ME/CFS, what criteria should be used to establish a clinical diagnosis?

I.1.5 Why this is important

There is an ongoing discussion in the ME/CFS community about which diagnostic criteria are best and which should be used in the identification and diagnosis of ME/CFS. The factors influencing these discussions are the broadness of the inclusion criteria, the definition of some of the symptoms, and the usability of the criteria as a clinical tool. There are concerns that many of the existing criteria do not accurately identify people with or without ME/CFS. This review described the seven diagnostic criteria for adults and two diagnostic criteria for

children and young people that met the inclusion criteria set out in the protocol. Currently there is no validated diagnostic criteria for ME/CFS and this leads to confusion about which criteria to use.

People with ME/CFS report delays in diagnosis and it is important to identify people with ME/CFS as early as possible to ensure they are given information to try to prevent worsening of symptoms and any further deterioration of health. Research has highlighted that many healthcare professionals lack the confidence and knowledge to recognise and diagnose ME/CFS and can find it difficult to distinguish from other conditions. Validated diagnostic criteria that accurately identify ME/CFS will support healthcare professionals to identify people who have ME/CFS and rule out those who do not.

I.1.61 Rationale for research recommendation / modified PICO

Research objectives	Population: Adults, children and young people with suspected ME/CFS Research objectives To validate the NICE 2020 consensus criteria for ME/CFS.Stage 1: To test the diagnostic ability of the criteria in UK specialist ME/CFS clinics and refine the criteria Stage 2: To ensure the diagnostic criteria are easy to understand by potential users Stage 3: Feasibility testing of a self/parent-complete diagnostic criteria questionnaire
Importance to patients or the population	At present there are no validated diagnostic criteria for ME/CFS and healthcare professionals report confusion over which criteria to use. This leads to delays in diagnosis and misdiagnosis and results in people not receiving appropriate care for ME/CFS. Validated criteria will lead to quicker access to care and should lead to better outcomes for people with ME/CFS and their families.
Relevance to NICE guidance	Good quality research in this area might allow NICE to recommend validated diagnostic criteria for the accurate detection of ME/CFS.
Relevance to the NHS	Recommendations for validated diagnostic criteria for ME/CFS will offer clinicians clearer guidance on how to diagnose ME/CFS.
National priorities	None
Current evidence base	There is an ongoing discussion in the ME/CFS community about which diagnostic criteria are best and which should be used in the identification and diagnosis of ME/CFS. The factors influencing these discussions are the broadness of the inclusion criteria, the definition of some of the symptoms, and the usability of the criteria as a clinical tool. This review described the seven diagnostic criteria for adults and two diagnostic criteria for children and young people that met the inclusion criteria set out in the protocol. None of the criteria were optimal and all had limitations related to their inclusion and exclusion criteria.
Equality	The recommendation is unlikely to impact on equality issues.
Study design	**Stage 1: To test the diagnostic ability of the criteria in UK specialist ME/CFS clinics and refine the criteria**

	Study design: The diagnostic ability of the agreed diagnostic set will be tested in a multi-centre case-control study. Cases will be defined as people with ME/CFS with a ME/CFS specialist diagnosis of ME/CFS and controls form a healthy population. Multivariate conditional logistic regression modelling will be used to determine the best predictive model to diagnose ME/CFS. **Stage 2: To ensure the diagnostic criteria are easy to understand by potential healthcare professional users** Study design: qualitative, interviews, surveys, focus groups **Stage 3: Feasibility testing of a self/parent-complete diagnostic criteria questionnaire** Study design: qualitative, interviews, surveys, focus groups
Feasibility	The proposed research can be carried out on a realistic timescale and at a reasonable cost.
Other comments	none
Importance	Low: the research is of interest and will fill existing evidence gaps.

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