

Appendix A: Pre-consultation summary of evidence from surveillance

10-year surveillance (2017) – [Chronic fatigue syndrome/myalgic encephalomyelitis \(or encephalopathy\)](#) (2007) NICE guideline CG53

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Summary of evidence from surveillance

General principles of care

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| <p>Q – 01 What are the information needs of healthcare professionals, patients and carers?</p> <p>Q – 02 What are the support needs of healthcare professionals, patients and carers?</p> |
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Recommendations derived from this question

Shared decision-making

- 1.1.1.1 Shared decision-making between the person with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) and healthcare professionals should take place during diagnosis and all phases of care. The healthcare professional should:
- Acknowledge the reality and impact of the condition and the symptoms.
 - Provide information about the range of interventions and management strategies as detailed in this guideline (such as the benefits, risks and likely side effects).
 - Provide information on the possible causes, nature and course of CFS/ME.
 - Provide information on returning to work or education.
 - Take account of the person's age (particularly for children younger than 12 years), the severity of their CFS/ME, their preferences and experiences, and the outcome of previous treatment(s).
 - Offer information about local and national self-help groups and support groups for people with CFS/ME and their carers (see also the NHS Expert Patients Programme*).
- 1.1.1.2 When providing care for children and young people, healthcare professionals should follow best practice as described in the national service frameworks for children for England or for Wales**.
- 1.1.1.3 Healthcare professionals should be aware that – like all people receiving care in the NHS – people with CFS/ME have the right to refuse or withdraw from any component of their care plan without this affecting other aspects of their care, or future choices about care.
- 1.1.1.4 Healthcare professionals should recognise that the person with CFS/ME is in charge of the aims and goals of the overall management plan. The pace of progression throughout the course of any intervention should be mutually agreed.

- 1.1.1.5 Healthcare professionals should provide diagnostic and therapeutic options to people with CFS/ME in ways that are suitable for the individual person. This may include providing domiciliary services (including specialist assessment) or using methods such as telephone or email.

Support and information

- 1.1.2.1 To facilitate effective management of the condition, healthcare professionals should aim to establish a supportive and collaborative relationship with the person with CFS/ME and their carers. Engagement with the family is particularly important for children and young people, and for people with severe CFS/ME.
- 1.1.2.2 A named healthcare professional should be responsible for coordinating care for each person with CFS/ME.
- 1.1.2.3 Healthcare professionals should provide accurate information to people at all stages of CFS/ME, starting from when a diagnosis is first being considered. This should be tailored to the person's circumstances, including the stage and duration of the condition, symptoms experienced and relevant personal and social factors.
- 1.1.2.4 Information should be available in a variety of formats if appropriate (printed copy, electronic and audio), which people with CFS/ME and their carers can refer to at home and in the clinical setting.

Provision of care

- 1.1.3.1 Healthcare professionals responsible for caring for people with CFS/ME should have appropriate skills and expertise in the condition.
- 1.1.3.2 Every person diagnosed with CFS/ME should be offered:
- information about the illness (see [section 1.1.2](#))
 - acceptance and understanding
 - assistance negotiating the healthcare, benefits and social care systems
 - assistance with occupational activities including work and education if appropriate (see [section 1.4.5](#)).
- 1.1.3.3 An individualised management plan should be developed with the person with CFS/ME, and their carers if appropriate. The plan should be reviewed and changes documented at each contact. It should include:
- relevant symptoms and history
 - plans for care and treatment, including managing setbacks/relapses
 - information and support needs
 - any education, training or employment support needs
 - details of the healthcare professionals involved in care and their contact details.

* For more information see [Expert Patients Programme](#) or [Education Programme for Patients Wales](#).

** Available from the [Department of Health](#) (England; this framework includes an exemplar pathway for CFS/ME) and [NHS Wales](#).

Surveillance decision

This review question should not be updated.

Shared decision-making

3-year surveillance summary

No relevant evidence was identified.

10-year surveillance summary

A qualitative study¹ (n=19 participants with CFS/ME) was nested within a randomised controlled trial (RCT) of 2 nurse-led therapist interventions. The aim of the qualitative study was to establish what factors were important for

people with CFS/ME to engage in the pragmatic rehabilitation tested by this RCT. The study also made recommendations to general practitioners (GPs) on preparing patients for referral to the intervention. The results showed that those factors were:

- ensuring that the patient feels accepted and believed
- patient's acceptance of having CFS/ME
- treatment model matches patient CFS/ME model

The authors concluded that GPs should explore the patient's illness beliefs before referral to maximise patient engagement in therapy.

A review and meta-synthesis of 34 qualitative studies² performed a multi-perspective examination of CFS/ME. Three thematic areas were found:

- experiences of people with CFS/ME, such as the influence of CFS/ME on identity, functioning, and coping;
- experiences of physicians, such as lack of awareness about CFS/ME and the need for improvement in educational resources;
- themes that intersect both of these groups, such as tensions about diagnosis and stigmatisation

It was concluded that physicians could improve diagnosis and treatment of CFS/ME through insight from the experiences of people with CFS/ME.

Topic expert feedback

NICE was made aware of the Supreme Court decision in the case of *Montgomery v Lanarkshire Health Board* (2015) regarding the law change to consent to treatment³. The judgment includes the statement that 'An adult person of sound mind is entitled to decide which, if any, of the available forms of treatment to undergo, and her consent must be obtained before treatment interfering with her bodily integrity is undertaken. The doctor is therefore under a duty to take reasonable care to ensure that the patient is aware of any material risks involved in any recommended treatment, and of any reasonable alternative or variant treatments. The test of materiality is whether, in the circumstances of the particular case, a reasonable person in the patient's position would be likely to attach significance to the risk, or the doctor is or should reasonably

be aware that the particular patient would be likely to attach significance to it.'

It was also noted that NICE guidelines need to make patients and clinicians aware that the guidelines are not legally binding and only offer guidance.

Impact statement

During the 3-year surveillance review, a qualitative study concluded that GPs could elicit and explore patients' CFS/ME beliefs before referral to specialist care. Another qualitative study concluded that physicians could improve diagnosis and treatment of CFS/ME through the insight from the experiences of people with CFS/ME. It was considered that these studies supported current recommendations which state that shared-decision making should take place between people with CFS/ME and health professionals during diagnosis and all phases of care. The guideline also recommends that health professionals should acknowledge the reality and impact of the condition and the symptoms and that they should take account of the person's age, the severity of their CFS/ME, their preferences and experiences, and the outcome of previous treatment(s). The evidence identified through surveillance is supportive of this.

Some issues were raised around consent to treatment. NICE guideline CG53 includes the sections 'Your responsibility' and 'Patient-centred care' which explain in detail the considerations that healthcare professionals should make when implementing the guideline, including fully involving patients and carers in decision-making, providing appropriate information, and that the guideline is not mandatory. In addition, in section 1.6.2 'Cognitive behavioural therapy, graded exercise therapy and activity management programmes', recommendation 1.6.2.2 states that 'The rationale and content of the different programmes, including their potential benefits and risks, should be fully explained to the person with CFS/ME', and recommendation 1.6.2.3 states that 'Healthcare professionals should recognise that the person with CFS/ME is in charge of the aims of the programme. The choice of the programme, its components, and progression throughout the programme should be mutually agreed'. The guideline therefore already stresses the importance of consent, providing information about risks, involving patients in decisions, and that guidelines are

not mandatory. The Montgomery ruling is unlikely to have any impact on current recommendations.

New evidence is unlikely to impact on the guideline.

Support and information

3-year surveillance summary

A randomised controlled trial (RCT)⁴ compared a buddy programme for patients with CFS/ME with a control programme. Participants who received the buddy programme intervention showed reduction in fatigue severity and increase in vitality compared with control group. No significant changes between groups for physical functioning and stress were found. The buddy programme was implemented over a 4-month period, therefore, the long-term effects of the intervention were unknown.

A qualitative study⁵ aimed to list the perspectives of people with CFS/ME regarding their medical encounter with a general practitioner (n=177 participants). The results of a patient survey demonstrated that people with CFS/ME seemed unsatisfied with the interaction with their doctor.

10-year surveillance summary

No relevant evidence was identified.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

During the 3-year surveillance review, a randomised study reported short-term improvement on fatigue severity and vitality after a buddy programme for people with CFS/ME. However, the long-term effect on CFS/ME was not evaluated. A qualitative study showed that people with CFS/ME seemed unsatisfied with the interaction with their doctor. It was concluded that these studies supported current recommendations which already highlight the importance of providing support and information to people with CFS/ME. No new evidence was identified through the 10 year surveillance review to change this conclusion.

New evidence is unlikely to impact on the guideline.

Provision of care

3-year surveillance summary

A qualitative case study⁶ demonstrated that lack of acknowledgement and lack of knowledge from doctors about CFS/ME could lead to long-term uncertainty (n=12 participants with CFS/ME). The authors concluded that the development of evidence-based strategies for assessment and management were necessary.

A before-and-after study⁷ described a train-the-trainer education and promotion programme focusing on the evaluation, diagnosis and management of CFS/ME (n=79 primary care providers). The authors concluded that the programme was successful among the physicians and nurses involved in increasing their knowledge of CFS/ME and improving their perceived self-efficacy towards making a diagnosis.

A before-and-after study⁸ focused on education of healthcare professionals about CFS/ME. An educational programme was developed

whereby CFS/ME continuing education materials were distributed to healthcare professionals at conferences. The online version of the course was deemed more popular than the print version.

A before-and-after study⁹ developed an educational intervention programme to improve student doctors understanding of CFS/ME. Following the programme there was some improvement among the participants in their willingness to treat patients with CFS/ME.

A qualitative study¹⁰ investigated the impact of an informational intervention among GPs focusing on using cognitive behavioural therapy (CBT) for management of CFS/ME (n=301 participants). The intervention involved distribution of written information about CFS/ME in addition to informational group sessions. The authors concluded that these methods were suitable and efficient for informing GPs about CFS/ME and for

stimulating GPs to refer people with CFS/ME for CBT.

A qualitative study¹¹ investigated how patient (n=24 people with CFS/ME) and physician (n=14 family physicians) knowledge of CFS/ME could affect the primary care consultation. The results of the study highlighted that physicians often obtained information about CFS/ME from nonprofessional sources and that there was a need for evidence-based knowledge about CFS/ME.

10-year surveillance summary

A meta-synthesis of 21 qualitative studies¹² produced a multi-perspective description of barriers to the diagnosis and management of CFS/ME. The results showed that health professionals had reported a limited understanding of CFS/ME and that some GPs were sceptical about the existence of CFS/ME if they worked with the biomedical model. On the contrary, GPs providing a diagnosis were more likely to work with a broader multifactorial model of CFS/ME.

A qualitative study nested within an RCT¹³ explored the experiences and acceptability of 2 different psychological interventions for CFS/ME (pragmatic rehabilitation and supportive listening) from the perspectives of nurses (n=3 participants), their supervisors (n=3 participants), and patients (n=46 participants) in primary care. Four challenges were identified with a potential to cause tension between therapist and patient:

- 'being a novice therapist'
- 'engaging patients in the therapeutic model'
- 'dealing with emotions'
- 'the complexity of primary care'.

Topic expert feedback

Topic experts highlighted that there seems to be considerable ongoing public and media interest in CFS/ME and referred to an internet communication about the provision of care for CFS/ME¹⁴. The communication provides comments about the biological basis of CFS/ME.

Topic experts also highlighted that parents of children with CFS/ME have been blamed for refusing CFS/ME treatment when children deteriorate after being treated with CBT/graded exercise therapy (GET)¹⁵ as recommended by NICE guideline CG53.

Topic experts referred to a national survey¹⁶ reporting that there is variation in the provision of NHS specialist CFS/ME services in England, including some evidence of inequity in accessing specialist services.

Impact statement

Through surveillance, a qualitative study found that doctors' acknowledgement and knowledge about CFS/ME was important for the management of CFS/ME. Three before-and-after studies and a qualitative study evaluated educational programmes for primary care providers, healthcare professionals, and student doctors. The first before-and-after study showed increased knowledge about CFS/ME improved self-efficacy in making a diagnosis in physicians and nurses. The second before-and-after study reported that an online course was more popular than a print course. The third before-and-after study showed improvement in student doctors in their willingness to treat people with CFS/ME. The qualitative study concluded that written information and informational group sessions were suitable and efficient for informing GPs about CFS/ME and for stimulating GPs to refer people with CFS/ME for CBT. A meta-synthesis of qualitative studies showed that from a GP's perspective, having a biomedical model limited their understanding and belief of CFS/ME. On the contrary, having a broader multifactorial model of CFS/ME helped GPs to provide a diagnosis of CFS/ME. A qualitative study identified that therapist inexperience could cause tension between them and people with CFS/ME receiving the therapy.

It was considered that these studies supported current recommendations regarding the provision of care. The guideline recommends that healthcare professionals responsible for caring for people with CFS/ME should have appropriate skills and expertise in the condition. Regarding the training programmes for healthcare professionals, there are no current recommendations about training. During guideline development, the committee noted that healthcare professionals need to have an appropriate level of training in CFS/ME when providing care to people with CFS/ME. The evidence identified through surveillance highlights the importance of training in CFS/ME among healthcare professionals and supports the recommendation which states that healthcare professionals responsible for caring for people with CFS/ME should have

appropriate skills and expertise in the condition. Regarding the care for children and young people, NICE guideline CG53 recommends that when providing care for children and young people, healthcare professionals should follow best practice as described in the national service frameworks for children for England or for Wales. Therefore, it was considered that current recommendations related to the care for children and young people were not likely to be affected.

Although there was some evidence of inequity in accessing specialist services, issues with provision and uptake of services is outside the scope of the surveillance process. The guideline already recommends referral to specialist care.

New evidence is unlikely to impact on the guideline.

Presentation

Q – 03 What are the existing case definitions for CFS/ME in adults and children? What evidence exists to substantiate or validate these case definitions?

Recommendations derived from this question

Presenting symptoms suspicious of CFS/ME

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
 - 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.

- 1.2.1.3 Healthcare professionals should be aware that the symptoms of CFS/ME fluctuate in severity and may change in nature over time.
- 1.2.1.4 Signs and symptoms that can be caused by other serious conditions ('red flags') should not be attributed to CFS/ME without consideration of alternative diagnoses or comorbidities. In particular, the following features should be investigated*:
- localising/focal neurological signs
 - signs and symptoms of inflammatory arthritis or connective tissue disease
 - signs and symptoms of cardiorespiratory disease
 - significant weight loss
 - sleep apnoea
 - clinically significant lymphadenopathy.

* Follow ['Referral guidelines for suspected cancer'](#) (NICE clinical guideline 27) or other NICE guidelines as the symptoms indicate.

Surveillance decision

This review question should not be updated.

Symptoms of CFS/ME

3-year surveillance summary

A study¹⁷ described a set of revised Canadian CFS/ME criteria for clinical case definition. As this was a descriptive study it is not clear if the diagnostic reliability and validity of this revised case definition was tested.

A cross-sectional study¹⁸ assessed sleep quality and intensity of fatigue in participants with CFS/ME and in healthy controls. The results of the study indicated that a sleep quality misperception exists in CFS/ME shown by the contrast in results between subjective and objective sleep quality in participants with CFS/ME.

A comparative study¹⁹ evaluated whether participants with CFS/ME (n=12 participants with fibromyalgia (FM) and n=14 participants without FM) had elevated rates of sleep-disturbed breathing or periodic leg movement disorder compared to 26 healthy participants. CFS/ME participants (with and without FM) felt sleepier and more fatigued than controls after a night's sleep. Rates of sleep-disturbed breathing or periodic leg movement disorder were not reported in the abstract.

A qualitative study²⁰ assessed a case definition for Italian patients with CFS/ME. The data highlighted persistent fatigue in addition to a clinical syndrome with infectious, neurological and rheumatological characteristics.

A qualitative study²¹ described the development of an epidemiological case-definition to distinguish CFS/ME from other chronic fatiguing conditions. However, it was not clear from an assessment of the abstract if diagnostic validity and reliability were tested.

A qualitative study²² aimed to test construct validity across diagnostic categories for CFS/ME from international epidemiological and clinical research data (33 studies in 21 countries including people with chronic fatigue [n=2,013 participants] and people with CFS/ME [n=1,958 participants]). The results showed a 5-factor model of key symptom domains which included musculoskeletal pain/fatigue, neurocognitive difficulties, inflammation, sleep disturbance/fatigue and mood disturbance. The authors concluded that the construct validity was supported by data from existing international datasets.

A study²³ compared severe versus moderate criteria for the paediatric case definition for CFS/ME (n=33 paediatric patients with CFS/ME, n=21 youth without CFS/ME). The results indicated that the paediatric case definition was able to distinguish between severe and moderate manifestations of CFS/ME and was also able to distinguish between individuals with CFS/ME and controls based on the scores of symptoms in 6 major categories: fatigue, post-exertional malaise, sleep, pain, neurocognitive difficulties, and

autonomic/neuroendocrine/immune manifestations.

A case series²⁴ investigated breathing behaviour during coping responses towards CFS/ME (n=30 participants). This study suggested that a coping response of hostile resistance triggered hyperventilation contributing to the clinical picture of CFS/ME.

A cohort study²⁵ found that participants with CFS/ME (n=38 participants) had significantly lower blood pressure and abnormal diurnal blood pressure regulation compared to normal controls (n=120 participants).

A comparative study²⁶ included a consecutive sample of adolescents with CFS/ME (n=15 participants) and healthy adolescents (n=57 participants) investigating thermoregulatory responses dependent on catecholaminergic effector systems in the participants. The results showed that adolescents with CFS/ME had abnormal catecholaminergic-dependent thermoregulatory responses both at rest and during local skin cooling.

A case series²⁷ compared participants with CFS/ME, multiple chemical sensitivity (MCS) and fibromyalgia (FM) to determine the extent of overlapping diagnostic criteria (n=114 participants who met criteria for CFS/ME). Nearly half of participants met criteria for CFS/ME alone, the rest of participants met criteria for 2 conditions (CFS/ME-MCS or CFS/ME-FM) or for the 3 conditions (CFS/ME-MCS-FM). The results showed some overlapping between CFS/ME, MCS, and FM.

A case series²⁸ did a 2-year follow-up of participants with CFS/ME and comorbid psychiatric disorders (n=70 participants). The prevalence of comorbid psychiatric disorders including major depressive disorders was found to be relatively high among individuals with CFS/ME.

A comparative study²⁹ investigated personality characteristics in people with CFS/ME (n=211 participants) compared to healthy people (n=90 participants). The authors concluded that patients displaying greater neuroticisms and poorer social and communication skills tended to show more severe symptoms of CFS/ME.

A Canadian national health survey³⁰ identified factors associated with depression among people with CFS/ME (n=1,045 participants).

Depression was associated with lower levels of self-esteem.

A comparative co-twin control study³¹ was conducted in 22 pairs of monozygotic twins, in which 1 twin met strict criteria for CFS/ME and the co-twin was healthy. Results indicated that twin groups had similar intellectual and visual memory functioning, but fatigued twins exhibited decreases in motor functions, speed of information processing, verbal memory, and executive functioning.

A meta-analysis³² examined cognitive functioning in people with CFS/ME in order to identify the pattern and magnitude of any deficits that are associated with this condition. The authors concluded that CFS/ME participants demonstrated moderate to large impairments in simple and complex information processing speed and in tasks requiring working memory over a sustained period of time.

A comparative study³³ aimed to describe the prevalence and type of anxiety symptoms in children with CFS/ME compared with a normal European population (n=164 participants). Although anxiety symptoms were found to be high in CFS/ME, particularly in teenage girls, it did not appear to be associated with school attendance or other measures of disability. Separation anxiety and social phobia were the most clearly elevated in paediatric CFS/ME.

A comparative study³⁴ used an activity log, which described patterns of daily behaviour, over the course of 2 days to examine whether differences existed in the pattern, intensity, and qualitative nature of activity among those with CFS/ME (n=30 participants), major depressive disorder (MDD) (n=20 participants) and healthy controls (n=15 participants). Findings indicated that people with CFS felt fatigued more of the time, found activity to be fatiguing more of the time, and needed more rest during activity than people with MDD or healthy controls.

A case series³⁵ aimed to determine whether individuals with CFS/ME could be classified into subgroups according to the types of fatigue they experienced (n=100 participants with CFS/ME). Participants were classified according to CFS/ME severity using a 3-factor solution (low, moderate, severe) or a 5-factor solution (low, moderate, severe plus sublevels of moderate and severe groups). The results of the study highlighted the heterogeneous fatigue patterns of participants with CFS/ME and

indicated that patients could be classified into meaningful subgroups.

10-year surveillance summary

No relevant evidence was identified.

Topic expert feedback

Topic experts referred to a list of research findings and papers worldwide and categorisation of biological abnormalities and dysfunctions and infections found in ME³⁶.

Impact statement

During the 3-year surveillance, evidence was found about symptoms associated with CFS/ME such as sleep disturbance; persistent fatigue; a clinical syndrome with infectious, neurological and rheumatological characteristics; musculoskeletal pain/fatigue; neurocognitive difficulties; inflammation; mood disturbance; post-exertional malaise; autonomic/neuroendocrine/immune manifestations; hyperventilation; abnormal blood pressure; abnormal catecholaminergic-

dependent thermoregulatory responses; multiple chemical sensitivity; fibromyalgia; major depressive disorders; neuroticisms; and poorer social and communication skills. The evidence also showed that there seemed to be a misperception about sleep quality in people with CFS/ME. Finally, this evidence also showed the possibility of classifying fatigue into 5 groups including 3 main groups of low, moderate and severe fatigue and subgroups of moderate and severe fatigue. It was considered that this evidence was not likely to impact current recommendations regarding symptoms/characteristics for CFS/ME because the majority of symptoms highlighted in the evidence were already listed by the guideline recommendations. No new evidence was identified through the 10 year surveillance review to change this conclusion.

New evidence is unlikely to impact on the guideline.

Presentation

Diagnosis

Q – 04 Are there any substantiated or validated evaluations to support the diagnosis of CFS/ME in adults and children?

Subquestion

In people presenting with early suspected CFS/ME (before 6 months) what are the risk factors/prognostic flags that might be linked with progression to CFS/ME?

Recommendations derived from this question

History, examinations and investigations

- 1.2.2.1 A full history (including exacerbating and alleviating factors, sleep disturbance and intercurrent stressors) should be taken, and a physical examination and assessment of psychological wellbeing should be carried out.
- 1.2.2.2 A child or young person who has symptoms suggestive of CFS/ME should be referred to a paediatrician for assessment to exclude other diagnoses within 6 weeks of presentation.
- 1.2.2.3 The following tests should usually be done:
 - urinalysis for protein, blood and glucose
 - full blood count
 - urea and electrolytes
 - liver function

- thyroid function
- erythrocyte sedimentation rate or plasma viscosity
- C-reactive protein
- random blood glucose
- serum creatinine
- screening blood tests for gluten sensitivity
- serum calcium
- creatine kinase
- assessment of serum ferritin levels (children and young people only).

Clinical judgement should be used when deciding on additional investigations to exclude other diagnoses.

- 1.2.2.4 Tests for serum ferritin in adults should not be carried out unless a full blood count and other haematological indices suggest iron deficiency.
- 1.2.2.5 Tests for vitamin B12 deficiency and folate levels should not be carried out unless a full blood count and mean cell volume show a macrocytosis.
- 1.2.2.6 The following tests should not be done routinely to aid diagnosis:
- the head-up tilt test
 - auditory brainstem responses
 - electrodermal conductivity.
- 1.2.2.7 Serological testing should not be carried out unless the history is indicative of an infection. Depending on the history, tests for the following infections may be appropriate:
- chronic bacterial infections, such as borreliosis
 - chronic viral infections, such as HIV or hepatitis B or C
 - acute viral infections, such as infectious mononucleosis (use heterophile antibody tests)
 - latent infections, such as toxoplasmosis, Epstein–Barr virus or cytomegalovirus.

Re-assessment before diagnosis

- 1.2.4.1 If symptoms do not resolve as expected in a person initially suspected of having a self-limiting condition, primary healthcare professionals should listen carefully to the person's and their family and/or carers' concerns and be prepared to reassess their initial opinion.
- 1.2.4.2 If considering the possibility of CFS/ME or another serious alternative condition, primary healthcare professionals should consider discussion with a specialist if there is uncertainty about the interpretation of signs and symptoms and whether a referral is needed. This may also enable the primary healthcare professional to communicate their concerns and a sense of urgency to secondary healthcare professionals if symptoms are unusual.

Making a diagnosis

- 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.
- 1.3.1.2 When a diagnosis of CFS/ME is made, healthcare professionals should provide honest, realistic information about CFS/ME and encourage cautious optimism.
- Most people with CFS/ME will improve over time and some people will recover and be able to resume work and normal activities.
 - However, others will continue to experience symptoms or relapse and some people with severe CFS/ME may remain housebound.

- The prognosis in children and young people is more optimistic.
- 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
 - chronic pain.

Surveillance decision

This review question should not be updated.

Diagnosis

3-year surveillance summary

A longitudinal study³⁷ aimed to determine whether an initial diagnosis of FM was associated with non-improvement of CFS/ME (n=94 female participants). The results of the study indicated that participants with CFS/ME and FM were at greatest risk of negative outcomes.

10-year surveillance summary

In 2015, 3 US reports indicated that changes in diagnostic criteria were likely to happen which could have an impact on NICE guideline CG53 recommendations. The reports were evaluated by the surveillance team in October 2015. The following paragraphs show a summary of the reports and the evaluation from the surveillance team.

Report 1

The Agency of Healthcare Research and Quality (AHRQ) report³⁸ concluded that

- none of the current diagnostic methods have been adequately tested to identify patients with CFS/ME when diagnostic uncertainty exists

The AHRQ report was updated in 2016³⁹. The purpose of the update was to assess the impact of studies using the Oxford case definition on conclusions and to assess the impact of separating studies of CBT from other counselling and behavioural interventions. A reduced strength of evidence was found when studies on CBT were distinguished from other counselling therapies as well as when studies using the Oxford case definition were excluded.

Report 2

The Institute of Medicine (IOM) report⁴⁰ considered the diagnostic criteria for CFS/ME and proposed the following:

Diagnosis requires that the patient have the following 3 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 2 following manifestations is also required:

1. cognitive impairment* or
2. orthostatic intolerance

* Frequency and severity of symptoms should be assessed. The diagnosis of CFS/ME should be questioned if patients do not have these symptoms at least half of the time with moderate, substantial, or severe intensity.

Report 3

The report⁴¹ of the US Department of Health & Human Services (HHS) Chronic Fatigue Syndrome Advisory Committee made a number of recommendations for a US audience on the need for further research in this field, particularly around:

- biomarkers and objective diagnostic tests
- gaps in basic, translational, clinical and epidemiological research to improve the understanding of the condition(s)

- research on treatments for people meeting newly proposed diagnostic characteristics
- standardised assessment and measurement tools.

The Committee also made some amendments to the proposed diagnostic criteria in the IOM report, including changing ‘unrefreshing sleep’ to ‘sleep disturbances’, added some features, expanded definitions, and recommended a period of 2 years’ validation of these. The report made a number of recommendations regarding treatment and care, but also recommended the development of clinical practice guidelines.

A systematic review⁴² examined methods to diagnose CFS/ME in adults (44 studies). Nine case definitions were found. The authors reported that people meeting criteria for ME represented a more symptomatic subset of the broader CFS/ME population. They also found that the evaluation of validity and generalisability of self-reported scales of CFS/ME symptoms was lacking.

A study⁴³ performed targeted broad-spectrum metabolomics to gain insights into the biology of CFS (n=45 participants with CFS/ME; n=39 participants without CFS/ME). There was a high probability to diagnose CFS/ME using 8 metabolites in men and 13 metabolites in women.

A study⁴⁴ hypothesised that changes in microRNA expression in patient’s leukocytes may be useful diagnostic biomarkers and that could be detected in the peripheral blood of CFS/ME patients (n=45 participants). It was concluded that potential diagnostic biomarkers could be the altered microRNA expression in the peripheral blood mononuclear cells of CFS/ME patients.

A study⁴⁵ explored the shift in discriminatory cytokines across women with CFS/ME separated by duration of illness and age (n=68 participants). There were 3 subgroups: 1) 18 years or younger and 2 or less years with CFS/ME; 2) 18-50 years and 7 years with CFS/ME; 3) 50 years or older and average of 11 years with CFS/ME. It was concluded that the preliminary results suggested interleukin 1 alpha (IL-1 α) 6 and 8 adjusted for CFS/ME duration might serve as robust biomarkers, independent of age, in screening for CFS/ME.

A case-control study⁴⁶ aimed to determine if spectral coherence (computational derivative of spectral analysis of the electroencephalogram

[EEG]) could differentiate between people with CFS/ME, healthy people, and people with depression (n=632 participants). The results showed that most participants were correctly classified as unmedicated people with CFS/ME, unmedicated healthy people, and people with depression. However, the model was less accurate identifying people with CFS/ME taking psychoactive medications. It seems that there is implication of the temporal lobe in CFS/ME pathophysiology.

A cross-sectional survey⁴⁷ aimed to describe epidemiological characteristics in people with CFS/ME (n=535 participants). Most of the participants were female, Caucasian, highly educated with a mean age of 46 years. A third of participants met the Fukuda CFS criteria, another third met both the Fukuda and International Consensus Criteria. The rest of participants did not meet these criteria or were not considered to have CFS/ME due to exclusionary conditions.

Topic expert feedback

NICE was made aware of new evidence on metabolomics⁴³; microRNAs⁴⁴; and cytokines⁴⁵ to diagnose CFS/ME. Topic experts highlighted new evidence on the implication of the temporal lobe in CFS/ME pathophysiology⁴⁶; and epidemiological characteristics in people with CFS/ME⁴⁷. This evidence has been summarised in the 10 year surveillance summary section.

Feedback suggested there may be differences between the NHS and private practice in availability of personalised biological treatments.

Regarding the Oxford case definition (which only requires 6 months of chronic fatigue and no other symptoms), NICE was made aware of the National Institutes of Health (NIH) Pathways to Prevention Workshop⁴⁸ which ‘called for Oxford criteria to be retired and stating Oxford criteria could impair progress and cause harm’. Feedback suggested that ‘the reason is that any results could not accurately be extrapolated to people with ME/CFS specifically. This is especially so for treatments, such as CBT and GET, that are likely to be effective for many people suffering from other fatiguing illnesses.’ It was further suggested that NICE guidelines should omit inclusion of studies that utilise Oxford criteria in evidence review for treatment recommendations.

NICE was also made aware of a newspaper article⁴⁹ reporting on new research investigating biomarkers for CFS/ME.

Additionally, topic experts commented on the 3 US reports on diagnostic criteria referred to in the 10-year surveillance summary above. It was noted that 2 of the reports requested a 2–5 year period going forward in which the validation and development of new criteria should take place. Experts were not aware of any research activity validating any proposed new diagnostic criteria since the reports published in 2015.

The experts also gave their thoughts on the current status of diagnostic criteria in NICE guideline CG53 and elsewhere, in light of these reports. Their comments included:

- The HHS Chronic Fatigue Syndrome Advisory Committee state: 'A priority should be placed on developing biomarkers and diagnostic tests... research has neglected many of the biological factors underlying ME/CFS'. Whereas in the UK there may be increasing acceptance of CFS/ME in the umbrella of functional neurological disorders. Evidence to define a subset of patients with the condition who appear to share a common biomarker is currently limited. The criteria originally adopted by NICE were adequate and at present there is no compelling evidence of a need to change them.
- These new criteria will include more people with more heterogeneous conditions and if used for research there is a risk that aetiology and treatment will become more unclear. Excluding fear of exercise may be a concern as patients with any degree of disability from the condition may have some anxiety about over-exercising, and CFS/ME is a condition that can generate distress, fear and despair. There are no gold standards by which one set of criteria can be said to be better or worse than any other. There is a lack of research data using these new criteria and no dataset in which to test these them because they all operated exclusion criteria that would not apply in the new criteria. The existing NICE criteria should remain in the absence of compelling data to change. Concerns about diagnosis from some perspectives should be acknowledged, alongside that the developers of these proposed alternative

North American criteria have suggested further research is needed.

- Diagnostic criteria are necessary because there are no diagnostic tests for CFS/ME. In the scoping meeting prior to developing NICE guideline CG53, there was a discussion on this with near unanimous consensus from stakeholders supporting broadly defined diagnostic criteria. This was to allow the inclusion of the vast majority of people with CFS/ME, which more narrowly defined criteria would exclude. A corollary of this was that it allowed the inclusion of the majority of trials, which have typically used broad diagnostic criteria. The expert was unaware of concerns about inclusion criteria of trials in CFS/ME, and noted some trials have been analysed according to more than one set of diagnostic criteria. The NICE diagnostic criteria should not be changed at present and from a clinical perspective are pragmatic and useful. The expert was not aware of patients attending clinics having concerns about the NICE diagnostic criteria.
- Significant debate was noted in the patient community online and in social media about changing diagnostic practice. There are concerns about recruiting using NICE guidance which is considered too broad and inclusive. Options include a) recruiting to all trials using NICE criteria but obtaining sufficient data to determine which patients would be classified as having CFS/ME using other research criteria such as the CDC (Fukuda) diagnostic criteria. b) Recruiting patients to study biomarkers using broad (permissive) criteria such as those recommended by NICE with sufficient phenotyping to determine those who fulfill other criteria.

Impact statement

The longitudinal study indicating that participants with CFS/ME and FM were at greatest risk of negative outcomes was a single trial and further research is needed to confirm findings.

The authors of the systematic review examining methods to diagnose CFS/ME stated that of the 9 case definitions found, none have been adequately tested to identify patients with ME/CFS when diagnostic uncertainty exists. They noted that more definitive studies in broader populations are needed to address

these research gaps. This evidence is unlikely to affect the guideline.

There was also evidence on metabolites, microRNA and cytokines to diagnose CFS/ME, and that the temporal lobe might be implicated in CFS/ME pathophysiology. However, this evidence was reported by single studies and further research to confirm results is needed. The evidence is unlikely to be sufficient to affect current recommendations.

The cross-sectional survey describing epidemiological characteristics did not attempt to validate any diagnostic criteria and is unlikely to impact the guideline.

Regarding feedback received of potential differences between NHS and private practice in personalised biological treatments, evidence in this area is currently limited therefore no impact on the guideline is expected. The comments regarding the need for the Oxford criteria to be retired do not impact directly on the guideline because it recommends a different diagnostic approach than the Oxford criteria. In terms of NICE excluding studies using Oxford criteria from evidence reviews for the guideline, as one of the topic experts stated: broadly defined diagnostic criteria in the NICE guideline (which was supported by almost all stakeholders during scoping) allow the inclusion of the vast majority of people with CFS/ME, and a corollary of this was that it allowed the inclusion of the majority of trials, which have typically used broad diagnostic criteria. Further, topic experts had no concerns about the inclusion criteria of trials in CFS, and it was also noted by topic experts that there is no gold standard definition of chronic fatigue syndrome.

Finally, the 3 US reports were evaluated by the surveillance team with the following conclusions:

- There was no clear impact on the guideline recommendations from the AHRQ report because changes to diagnostic criteria might have implications for the applicability

of any research used to inform the current guideline. This report did not recommend a particular change.

- The proposals from the IOM report differed from the recommendations for features suggesting the possibility of CFS/ME in NICE guideline CG53 and from the approach to diagnosis in NICE guideline CG53. It was likely that the proposed criteria would also differ from the inclusion criteria for studies of interventions for people with CFS/ME. It was difficult to predict the effect this might have on the recommendations in NICE guideline CG53. However, it was worth noting that this was a proposal, and must be interpreted alongside the subsequent recommendations of the HHS Chronic Fatigue Syndrome Advisory Committee.
- Diagnostic criteria might change after the validation by the HHS Chronic Fatigue Syndrome Advisory Committee. It was also highlighted that one of the recommendations on treatment and care called for a 'Declaration that the disease is not the result of fear-based avoidance of activity and that CBT and GET for this purpose are inappropriate'. NICE guideline CG53 recommends individualised use of these interventions, and does not recommend any particular assumptions about the cause of CFS/ME. It was concluded that the impact of this statement was unclear.

Topic experts agreed with the conclusions of the surveillance team about the 3 US reports, and indicated that until and unless further research suggests otherwise, the NICE diagnostic criteria for CFS/ME remain valid.

The impact on CBT from the AHRQ report is discussed under [review question Q – 05](#).

New evidence is unlikely to change guideline recommendations.

Risk factors/prognostic flags

3-year surveillance summary

No relevant evidence was identified.

10-year surveillance summary

A study⁵⁰ measured exercise tolerance in adolescents with CFS and adolescents without CFS/ME 6 months after acute infectious mononucleosis (n=42 participants).

Adolescents with CFS had significantly lower

oxygen consumption and oxygen pulse (volume of oxygen consumed by the body per heartbeat) compared with adolescents without CFS/ME. The authors concluded it was uncertain whether these abnormal exercise findings were a cause or effect of CFS/ME.

A population-based case-control study⁵¹ compared gynaecological history events as risk factors for CFS/ME between women with CFS/ME and women without fatigue (n=84 participants). The following gynaecological events were significantly higher in women with CFS/ME compared to women without fatigue:

- pelvic pain unrelated to menstruation
- endometriosis
- pregnancies
- gynaecological surgeries.

It was concluded that further research was needed to clarify the chronologic and pathophysiological relationships between gynaecological history events and CFS/ME.

A prospective birth cohort study⁵² examined premorbid risk markers for CFS/ME (n=368 participants with CFS/ME at 42 years [n=127 self-reported CFS/ME, n=241 operationally defined CFS/ME]). The results were adjusted for psychopathology showing 3 risk markers associated with self-report CFS/ME: parental physical abuse, childhood gastrointestinal symptoms, and parental reports of many colds. A replication study of this birth cohort study⁵³ investigated associations between psychopathology, self-reported physical activity and self-reported CFS/ME. There were significant associations between premorbid psychopathology (at 23 and 33 years) and CFS/ME.

A retrospective observational case-control study⁵⁴ explored stressful situations associated with CFS/ME presentation (n=77 cases, n=77 controls). The following stressful life

events were significantly associated with CFS presentation:

- pregnancy,
- marital abuse and bullying,
- eating disorders,
- a car accident,
- economic problems, and
- changes in sleep habits.

The authors suggested these events should be taken into consideration when taking background information at CFS/ME presentation.

A longitudinal birth cohort study⁵⁵ was used to investigate risk factors for chronic disabling fatigue at 13 years (n=110 participants). The results showed that maternal anxiety and depression were associated with chronic disabling fatigue in adolescents 13 years old.

Topic expert feedback

Topic experts highlighted evidence on maternal anxiety and depression associated with chronic disabling fatigue in adolescents 13 years old⁵⁵. This evidence has been summarised in the 10 year surveillance summary section.

Impact statement

During the 10-year surveillance, evidence was found about potential prognostic factors that could be linked with progression to CFS/ME such as exercise tolerance; gynaecological events; premorbid psychopathology; stressful life events; plasma levels of the neurohumoral factors; maternal anxiety and depression. However, these were studies with small sample sizes. Therefore, it would be pertinent to wait for further evidence before including prognostic factors into current recommendations.

New evidence is unlikely to change guideline recommendations.

Differences between children and adults with CFS/ME

3-year surveillance summary

No relevant evidence was identified.

10-year surveillance summary

A study⁵⁶ investigated differences between young children (aged <12 years), adolescents (aged 12-18 years) and adults with CFS/ME.

Younger children were significantly less likely to have cognitive symptoms and significantly more likely to present with a sore throat. Adolescents were significantly more likely to have headaches and comorbid depression and less likely to have anxiety compared to adults.

Topic expert feedback

Topic expert highlighted that the General Medical Council (GMC) has stated that there is

no evidence to prove differences or similarities between children and adults with ME⁵⁷.

Impact statement

During the 10-year surveillance review, evidence reported differences between children, adolescents and adults with CFS/ME. This evidence was considered to support

guideline recommendations in that a paediatrician should make or confirm CFS/ME diagnosis in children or young people.

New evidence is unlikely to change guideline recommendations.

[General management strategies after diagnosis](#)

[Referral to specialist CFS/ME care](#)

[Specialist CFS/ME care](#)

[Management of setbacks/relapses](#)

Q – 05 Does the evidence show that any particular intervention or combination of interventions is effective in treatment, management or rehabilitation of adults and children with a diagnosis of CFS/ME?

Subquestion

In people presenting with early suspected CFS/ME what interventions might be effective in preventing progression to CFS/ME?

Recommendations derived from this question

General management strategies after diagnosis

Symptom management

- 1.4.1.1 There is no known pharmacological treatment or cure for CFS/ME. However, symptoms of CFS/ME should be managed as in usual clinical practice.
- 1.4.1.2 No research evidence was found to support the experience of some people with CFS/ME that they are more intolerant of drug treatment and have more severe adverse/side effects. However, if people with CFS/ME have concerns, healthcare professionals may consider starting drug treatment for CFS/ME symptoms at a lower dose than in usual clinical practice. The dose may be increased gradually, in agreement with the patient.
- 1.4.1.3 Specific drug treatment for children and young people with CFS/ME should be started by a paediatrician. However, prescribing may be continued in primary care, depending on the preferences of the patient and their carers, and local circumstances.
- 1.4.1.4 If a person experiences nausea as part of CFS/ME, this should be managed conventionally, including giving advice on eating little and often, snacking on dry starchy foods and sipping fluids. The use of anti-emetic drugs should be considered only if the nausea is severe.
- 1.4.1.5 Although exclusion diets are not generally recommended for managing CFS/ME, many people find them helpful in managing symptoms, including bowel symptoms. If a person with CFS/ME undertakes an exclusion diet or dietary manipulation, healthcare professionals should seek advice from a dietitian because of the risk of malnutrition.

Function and quality-of-life management

Sleep management

- 1.4.2.1 Healthcare professionals should provide tailored sleep management advice that includes:

- Explaining the role and effect of disordered sleep or sleep dysfunction in CFS/ME.
 - Identifying the common changes in sleep patterns seen in CFS/ME that may exacerbate fatigue symptoms (such as insomnia, hypersomnia, sleep reversal, altered sleep–wake cycle and non-refreshing sleep).
 - Providing general advice on good sleep hygiene*.
 - Introducing changes to sleep patterns gradually.
 - Regular review.
- 1.4.2.2 If sleep management strategies do not improve the person's sleep and rest, the possibility of an underlying sleep disorder or dysfunction should be considered, and interventions provided if needed.
- 1.4.2.3 Sleep management strategies should not include encouraging daytime sleeping and naps. People with CFS/ME should be advised that excessive sleep does not generally improve physical or mental functioning, and excessive periods of daytime sleep or frequent napping may further disrupt the sleep–wake cycle.

Rest periods

- 1.4.2.4 Rest periods are a component of all management strategies for CFS/ME. Healthcare professionals should advise people with CFS/ME on the role of rest, how to introduce rest periods into their daily routine, and the frequency and length appropriate for each person. This may include:
- Limiting the length of rest periods to 30 minutes at a time.
 - Introducing 'low level' physical and cognitive activities (depending on the severity of symptoms).
 - Using relaxation techniques (see [recommendation 1.4.2.6](#)).
- 1.4.2.5 Healthcare professionals should review the use of rest periods regularly as part of the patient's management plan.

Relaxation

- 1.4.2.6 Relaxation techniques appropriate to the person with CFS/ME should be offered for the management of pain, sleep problems and comorbid stress or anxiety. There are a number of different relaxation techniques (such as guided visualisation or breathing techniques) that can be incorporated into rest periods.

Pacing

- 1.4.2.7 People with CFS/ME have reported pacing to be helpful in self-managing CFS/ME. However, healthcare professionals should advise people with CFS/ME that, at present, there is insufficient research evidence on the benefits or harm of pacing.

Diet

See also recommendations on managing nausea ([1.4.1.4](#)) and bowel symptoms ([1.4.1.5](#)), and use of supplements ([1.4.7.2–4](#)).

- 1.4.3.1 Healthcare professionals should emphasise the importance of a well-balanced diet in line with 'The balance of good health'**. They should work with the person with CFS/ME to develop strategies to minimise complications that may be caused by nausea, swallowing problems, sore throat or difficulties with buying, preparing and eating food.
- 1.4.3.2 Healthcare professionals should emphasise the importance of eating regularly, and including slow-release starchy foods in meals and snacks. The physiological consequences of not doing so should be explained to the person with CFS/ME.

Equipment to maintain independence

- 1.4.4.1 For people with moderate or severe CFS/ME, providing or recommending equipment and adaptations (such as a wheelchair, blue badge or stairlift) should be considered as part of an overall management plan, taking into account the risks and benefits for the individual patient. This may help them to maintain their independence and improve their quality of life.

Education and employment

- 1.4.5.1 Having to stop their work or education is generally detrimental to people's health and well-being. Therefore, the ability of a person with CFS/ME to continue in education or work should be addressed early and reviewed regularly.
- 1.4.5.2 Healthcare professionals should proactively advise about fitness for work and education, and recommend flexible adjustments or adaptations to work or studies to help people with CFS/ME to return to them when they are ready and fit enough. This may include, with the informed consent of the person with CFS/ME, liaising with employers, education providers and support services, such as:
- occupational health services
 - disability services through Jobcentre Plus
 - schools, home education services and local education authorities
 - disability advisers in universities and colleges.
- 1.4.5.3 For people with CFS/ME who are able to continue in or return to education or employment, healthcare professionals should ensure, with the person's informed consent, that employers, occupational health or education institutions have information on the condition and the agreed management plan.

Education

- 1.4.5.4 Healthcare professionals should follow the guidance from the Department for Children, Schools and Families[†] on education for children and young people with medical needs, or equivalent statutory guidance.
- 1.4.5.5 Healthcare professionals should work closely with social care and education services to ensure a common understanding of the goals of the person with CFS/ME. The use of a flexible approach should be discussed, including home tuition and use of equipment that allows a gradual reintegration into education.
- 1.4.5.6 Time in education should not be used as a sole marker of progress of CFS/ME, and education should not be the only activity a person undertakes. There should be a balance between time spent attending school or college and doing homework, and time spent on home and social activities.

Employment

- 1.4.5.7 If possible, and with the informed consent of the person with CFS/ME, healthcare professionals should discuss employment issues with occupational health professionals, who will communicate with the person's manager or human resources representative. If there is no access to occupational health services, the responsible clinician should liaise with the employer directly^{††}.

Strategies that should not be used for CFS/ME

- 1.4.6.1 The following drugs should not be used for the treatment of CFS/ME:
- monoamine oxidase inhibitors
 - glucocorticoids (such as hydrocortisone)
 - mineralocorticoids (such as fludrocortisone)
 - dexamphetamine
 - methylphenidate
 - thyroxine
 - antiviral agents.
- 1.4.6.2 The following strategies should not be offered to people with CFS/ME:
- Advice to undertake unsupervised, or unstructured, vigorous exercise (such as simply 'go to the gym' or 'exercise more') because this may worsen symptoms.
 - Specialist management programmes (see [section 1.6](#)) delivered by practitioners with no experience in the condition.

- 1.4.6.3 Although there is considerable support from patients (particularly people with severe CFS/ME) for the following strategies, healthcare professionals should be aware that there is no controlled trial evidence of benefit:
- Encouraging maintenance of activity levels at substantially less than full capacity to reserve energy for the body to heal itself (sometimes known as the envelope theory).
 - Encouraging complete rest (cognitive, physical and emotional) during a setback/relapse.
- 1.4.6.4 Strategies for managing CFS/ME should not include:
- Prolonged or complete rest or extended periods of daytime rest in response to a slight increase in symptoms.
 - An imposed rigid schedule of activity and rest.

Complementary and supplementary therapies

- 1.4.7.1 There is insufficient evidence that complementary therapies are effective treatments for CFS/ME and therefore their use is not recommended. However, some people with CFS/ME choose to use some of these therapies for symptom control, and find them helpful.
- 1.4.7.2 There is insufficient evidence for the use of supplements – such as vitamin B12, vitamin C, co-enzyme Q10, magnesium, NADH (nicotinamide adenine dinucleotide) or multivitamins and minerals – for people with CFS/ME, and therefore they should not be prescribed for treating the symptoms of the condition. However, some people with CFS/ME have reported finding these helpful as a part of a self-management strategy for their symptoms.
- 1.4.7.3 People with CFS/ME who are using supplements should be advised not to exceed the safe levels recommended by the Food Standards Agency[‡].
- 1.4.7.4 Some people with CFS/ME need supplements because of a restricted dietary intake or nutritional deficiencies. Healthcare professionals should seek advice from a dietitian about any concerns.

Referral to specialist CFS/ME care

- 1.5.1.1 Any decision to refer a person to specialist CFS/ME care should be based on their needs, the type, duration, complexity and severity of their symptoms, and the presence of comorbidities. The decision should be made jointly by the person with CFS/ME and the healthcare professional.
- 1.5.1.2 Referral to specialist CFS/ME care should be offered:
- within 6 months of presentation to people with mild CFS/ME
 - within 3–4 months of presentation to people with moderate CFS/ME symptoms
 - immediately to people with severe CFS/ME symptoms.

Specialist CFS/ME care

- 1.6.1.1 After a patient is referred to specialist care, an initial assessment should be done to confirm the diagnosis.
- 1.6.1.2 If general management strategies (see [section 1.4](#)) are helpful for a person with CFS/ME, these should be continued after referral to specialist CFS/ME care.

Cognitive behavioural therapy, graded exercise therapy and activity management programmes

Choosing and planning treatment

- 1.6.2.1 An individualised, person-centred programme should be offered to people with CFS/ME. The objectives of the programme should be to:
- sustain or gradually extend, if possible, the person's physical, emotional and cognitive capacity
 - manage the physical and emotional impact of their symptoms.
- 1.6.2.2 The rationale and content of the different programmes, including their potential benefits and risks, should be fully explained to the person with CFS/ME. Healthcare professionals should explain that no single strategy will be successful for all patients, or during all stages of the condition.

- 1.6.2.3 Healthcare professionals should recognise that the person with CFS/ME is in charge of the aims of the programme. The choice of the programme, its components, and progression throughout the programme should be mutually agreed and based on:
- the person's age, preferences and needs
 - the person's skills and abilities in managing their condition, and their goals (such as improvement or treatment of deterioration of symptoms, prevention of relapse or maintenance)
 - the severity and complexity of symptoms
 - physical and cognitive functioning.
- 1.6.2.4 Cognitive behavioural therapy (CBT) and/or graded exercise therapy (GET) should be offered to people with mild or moderate CFS/ME and provided to those who choose these approaches, because currently these are the interventions for which there is the clearest research evidence of benefit.
- 1.6.2.5 If a full CBT or GET programme is inappropriate or not available, components of CBT or GET should be offered, either individually or more effectively in combination with:
- activity management strategies (see [1.6.2.22](#))
 - sleep management (see [1.4.2.1–3](#))
 - relaxation techniques (see [1.4.2.6](#)).
- 1.6.2.6 The choice of programme, its components and progression through it should be reviewed regularly, taking into account the goals and abilities of the person with CFS/ME, and other approaches agreed as necessary.
- 1.6.2.7 Healthcare professionals should advise people with CFS/ME to contact them if they experience an increase in symptoms that lasts for longer than a few days after starting the specialist programme, or if symptoms are severe or distressing.

Cognitive behavioural therapy (CBT)

- 1.6.2.8 A course of CBT should be delivered only by a healthcare professional with appropriate training in CBT and experience in CFS/ME, under clinical supervision. The therapist should adhere closely to empirically grounded therapy protocols.
- 1.6.2.9 CBT should be offered on a one-to-one basis if possible.
- 1.6.2.10 CBT for a person with CFS/ME should be planned according to the usual principles of CBT, and should include:
- Acknowledging and validating the person's symptoms and condition.
 - Explaining the CBT approach in CFS/ME, such as the relationship between thoughts, feelings, behaviours and symptoms, and the distinction between causal and perpetuating factors.
 - Discussing the person's attitudes and expectations.
 - Developing a supportive and collaborative therapeutic relationship.
 - Developing a shared formulation and understanding of factors that affect CFS/ME symptoms.
 - Agreeing therapeutic goals.
 - Tailoring treatment to the person's needs and level of functioning.
 - Recording and analysing patterns of activity and rest, and thoughts, feelings and behaviours (self-monitoring).
 - Establishing a stable and maintainable activity level (baseline) followed by a gradual and mutually agreed increase in activity.
 - Challenging thoughts and expectations that may affect symptom improvement and outcomes.

- Addressing complex adjustment to diagnosis and acceptance of current functional limitations.
- Developing awareness of thoughts, expectations or beliefs and defining fatigue-related cognitions and behaviour.
- Identifying perpetuating factors that may maintain or exacerbate CFS/ME symptoms to increase the person's self-efficacy (sense of control over symptoms).
- Addressing any over-vigilance to symptoms and related checking or reassurance-seeking behaviours by providing physiological explanations of symptoms and using refocusing/distraction techniques.
- Problem solving using activity management and homework tasks to test out alternative thoughts or beliefs, such as undertaking pleasure and mastery tasks (tasks that are enjoyable and give a sense of accomplishment).
- Building on existing assertion and communication skills to set appropriate limits on activity.
- Managing sleep problems, for example by addressing any unhelpful beliefs about sleep, behavioural approaches to sleep disturbance, stress management, and/or relaxation training (see recommendations [1.4.2.1–6](#)).
- Treating any associated or comorbid anxiety, depression or mood disorder according to NICE clinical guidelines on these conditions (see [section 6](#)).
- Offering information on managing setbacks/relapses (see [section 1.7](#)).

Graded exercise therapy (GET)

- 1.6.2.11 GET should be delivered only by a suitably trained GET therapist with experience in CFS/ME, under appropriate clinical supervision.
- 1.6.2.12 GET should be offered on a one-to-one basis if possible.
- 1.6.2.13 People with mild or moderate CFS/ME should be offered GET that includes planned increases in the duration of physical activity. The intensity should then be increased when appropriate, leading to aerobic exercise (that is, exercise that increases the pulse rate).
- 1.6.2.14 GET should be based on the person's current level of activities (such as physical activity, daily routines, sleep patterns and frequency of setbacks/relapses) and emotional factors, vocational or educational factors and individual goals (details of these may be obtained from an activity diary). The programme should also include sleep and relaxation strategies (see recommendations [1.4.2.1–6](#)).
- 1.6.2.15 When planning GET, the healthcare professional should:
- Undertake an activity analysis to ensure that the person with CFS/ME is not in a 'boom and bust' cycle before they increase the time spent in exercise.
 - Discuss with the person the ultimate goals that are important and relevant to them. This might be, for example, a twice-daily short walk to the shops, a return to a previous active hobby such as cycling or gardening, or, for people with severe CFS/ME, sitting up in bed to eat a meal.
 - Recognise that it can take weeks, months or even years to achieve goals, and ensure that this is taken into account in the therapy structure (for example, by setting short- and medium-term goals).
 - Explain symptoms and the benefits of exercise in a physiological context.
- 1.6.2.16 When starting GET, the healthcare professional should:
- Assess the person's current daily activities to determine their baseline.
 - Agree with them a level of additional low-intensity exercise that is sustainable, independent of daily fluctuations in symptoms, and does not lead to 'boom and bust' cycles. This may be sitting up in bed or brushing hair, for example, for people with severe CFS/ME, or gentle stretches or a slow walk.

- Encourage them to undertake this exercise for at least 5 days out of 7, or build up to this level if and when possible.
- Advise them that this level of exercise may mildly increase symptoms for a few days (for example, a mild to moderate increase in stiffness and fatigue), explain why this may occur and discuss strategies to mitigate it.
- Offer information on the management of setbacks/relapses (see [section 1.7](#)).

Progressing with GET

- 1.6.2.17 When the low-intensity exercise can be sustained for 5 days out of 7 (usually accompanied by a reduction in perceived exertion), the duration should be reviewed and increased, if appropriate, by up to 20%. For example, a 5-minute walk becomes 6 minutes, or a person with severe CFS/ME sits up in bed for a longer period, or walks to another room more often. The aim is to reach 30 minutes of low-intensity exercise.
- 1.6.2.18 When the duration of low-intensity exercise has reached 30 minutes, the intensity of the exercise may be increased gradually up to an aerobic heart rate zone, as assessed individually by a healthcare professional. A rate of 50–70% maximum heart rate is recommended.
- 1.6.2.19 Exercise intensity should be measured using a heart rate monitor, so that the person knows they are within their target heart rate zone.
- 1.6.2.20 If agreed GET goals are met, exercise duration and intensity may be increased further if appropriate, if other daily activities can also be sustained, and in agreement with the person with CFS/ME.

Maintaining exercise

- 1.6.2.21 After completing a GET programme, the healthcare professional and the person with CFS/ME should continue working together to develop and build on strategies to maintain exercise. Support should be available, if needed, to enable the person to reinforce the learning and lifestyle changes made and continue GET beyond discharge.

Activity management

- 1.6.2.22 Activity management is a goal-oriented and person-centred approach tailored to the needs of the person with CFS/ME. It should include:
- Understanding that activities have physical, emotional and cognitive components, and identifying these components.
 - Keeping a diary that records cognitive and physical activity, daytime rest and sleep. This will help to set baseline levels of activity (a stable and sustainable range of functioning), identify patterns of over- and underactivity, and develop an activity/exercise strategy.
 - Establishing a baseline; specific activities may need to be increased or decreased while this is happening.
 - Gradually increasing activity above the baseline in agreement with the person.
 - Planning daily activities to allow for a balance and variety of different types of activity, rest and sleep. This may include making a weekly activity schedule.
 - Spreading out difficult or demanding tasks over the day or week.
 - Splitting activities into small achievable tasks according to the person's level of ability/functioning, followed by gradual increases in the complexity of the tasks.
 - Monitoring, regulating and planning activities to avoid a 'boom and bust' cycle.
 - Goal setting, planning and prioritising activities.
 - Explaining the role of rest in CFS/ME and helping the person work out how to build in rest periods and achieve a productive day (see recommendations [1.4.2.1–6](#)).
 - Regularly reviewing activity levels and goals.
 - Offering information on the management of setbacks/relapses (see [section 1.7](#)).

Pharmacological interventions for symptom control

- 1.6.3.1 If chronic pain is a predominant feature, healthcare professionals should consider referral to a pain management clinic.
- 1.6.3.2 Prescribing of low-dose tricyclic antidepressants, specifically amitriptyline, should be considered for people with CFS/ME who have poor sleep or pain. Tricyclic antidepressants should not be offered to people who are already taking selective serotonin reuptake inhibitors (SSRIs) because of the potential for serious adverse interactions.
- 1.6.3.3 Melatonin may be considered for children and young people with CFS/ME who have sleep difficulties, but only under specialist supervision because it is not licensed in the UK.

Management of setbacks/relapses

Preparing for a setback/relapse

- 1.7.1.1 People with CFS/ME should be advised that setbacks/relapses are to be expected as part of CFS/ME.
- 1.7.1.2 Healthcare professionals and people with CFS/ME should develop a plan for managing setbacks/relapses, so that skills, strategies, resources and support are readily available and accessible when needed. This plan may be shared with the person's carers, if they agree.

During a setback/relapse

- 1.7.2.1 Setbacks/relapses may be triggered by factors such as unexpected/unplanned activities, poor sleep, infection or stress. Healthcare professionals, in discussion with the person with CFS/ME, should try to identify the cause(s) of a setback/relapse, but it should be recognised that this may not always be possible.
- 1.7.2.2 When managing a setback/relapse, the management plan should be reviewed. Healthcare professionals should discuss and agree an appropriate course of action with the person with CFS/ME, taking into account:
 - the person's experience
 - possible causes of the setback/relapse, if known
 - the nature of the symptoms
 - the severity and duration of the setback/relapse
 - the current management plan.
- 1.7.2.3 When managing setbacks, healthcare professionals should put strategies in place that:
 - Include relaxation and breathing techniques.
 - Maintain activity and exercise levels if possible, by alternating activities with breaks and pacing activities, as appropriate.
 - Involve talking to families and carers, if appropriate.
 - Recognise distressing thoughts about setbacks/relapses such as 'this means I'll never get better', but encourage optimism.
 - Involve reconsidering and revising the levels and types of symptom control.
- 1.7.2.4 In some setbacks/relapses, it may be necessary to reduce, or even stop some activities and increase the frequency and/or duration of rest periods to stabilise symptoms and re-establish a baseline activity level. This should be discussed and agreed with the person with CFS/ME.
- 1.7.2.5 People with CFS/ME should be advised to minimise daytime sleep periods. However, healthcare professionals should recognise that this is not always possible, depending on the severity of a person's symptoms and the setback.

After a setback/relapse

- 1.7.3.1 After a setback/relapse, healthcare professionals should review the person's activity levels to re-establish a baseline and review the management plan. A gradual return, when possible, to previous exercise and functional routines should be encouraged. Activity should be increased gradually.
- 1.7.3.2 Healthcare professionals should advise on:

- Slowly decreasing the frequency and duration of rest periods.
- Continuing the use of relaxation techniques, even when the person with CFS/ME is beginning to feel better.

1.7.3.3 After a setback, healthcare professionals and people with CFS/ME should review the experience to determine, if possible, whether triggers can be managed in the future, and put strategies in place to do this.

* For general advice on sleep hygiene, see the [NHS Direct website](#).

** Food Standards Agency (2006) '[The balance of good health](#)'. London: Foods Standards Agency.

† See [Department for Education](#)

†† [NHS Plus](#) has produced guidance on the occupational aspects of the management of CFS/ME (search for 'chronic fatigue syndrome').

‡ See [Food Standards Agency](#)

Surveillance decision

This review question should not be updated.

Cognitive behavioural therapy

3-year surveillance summary

A systematic review⁵⁸ included 14 studies describing the clinical follow-up of patients following a diagnosis of CFS/ME. The authors concluded that full recovery from untreated CFS/ME was rare but improvement of symptoms was more frequent.

A meta-analysis of 2 CBT studies⁵⁹ (n=96 adults with CFS/ME, 1 study and n=32 adolescents with CFS/ME, 1 study) found that successful CBT treatment of CFS/ME reduced pain. Decrease in fatigue predicted a change in pain severity. Pain severity at baseline was predictive of a negative treatment outcome.

A meta-analysis of 2 RCTs⁶⁰ concluded that CBT might lead to a reduction in self-reported cognitive impairment, but not to improved neuropsychological test performance compared to no treatment (adults and adolescents with CFS/ME).

A meta-analysis of 13 RCTs⁶¹ (n=1,371 participants with CFS/ME) reported that CBT for CFS/ME tends to be moderately effective compared to no treatment.

A Cochrane review of 15 RCTs⁶² examined effectiveness and acceptability of CBT for CFS/ME, alone and in combination with other interventions, compared with usual care and other interventions such as other psychological therapies including relaxation, counselling, and education/support (n=1,043 adults with CFS/ME). CBT appeared to be effective in

reducing the symptoms of fatigue at post-treatment compared with usual care and other psychological therapies. The evidence base at follow up was limited to a small group of studies with inconsistent findings. It was concluded that further studies were required to inform the development of effective treatment programmes for people with CFS/ME.

A meta-analysis of 3 RCTs⁶³ examined frequency and severity of symptom deterioration during CBT for CFS/ME. Participants receiving CBT did not experience more frequent or more severe symptom deterioration compared to untreated participants. It was concluded that CBT might be a safe treatment for CFS/ME.

A meta-analysis of 3 RCTs⁶⁴ investigated the mechanism by which CBT (compared to no treatment) reduces fatigue in people with CFS/ME. The authors concluded that persistent increase in physical activity did not mediate the effect of CBT on fatigue.

An RCT⁶⁵ compared CBT aided by biofeedback against symptomatic treatment (n=92 adolescents with CFS/ME). Results showed that CBT aided by biofeedback improved individual strength, school attendance, and self-rated CFS/ME symptoms compared to symptomatic treatment.

A sample of participants from an RCT⁶⁶ was used to develop a measure to evaluate therapy process (CBT compared to counselling) and its relationship with outcome of self-reported fatigue symptoms (n=71 participants with chronic fatigue in primary care). The new

measure demonstrated some overlap between CBT and counselling. This study also showed the importance of emotional processing in patients with CFS/ME and how further research was necessary to better understand how this could be better facilitated.

An RCT evaluated 4 nurse-delivered non-pharmacologic interventions⁶⁷ in participants with CFS/ME (n= 114 participants). The interventions were CBT, cognitive therapy, anaerobic activity, and relaxation (control group). The study found interventions including CBT led to an increase in several areas of functioning.

An RCT⁶⁸ compared CBT against waiting-list (n=171 participants with CFS/ME). Intention-to-treat analysis showed a significant decrease in fatigue and disability after self-instruction combined with email contact for CBT compared to waiting list.

A study⁶⁹ assessed long-term outcomes of fatigue severity, physical functioning, and school attendance of an RCT comparing CBT with a waiting list (n=61 adolescents with CFS/ME). Fatigue severity of adolescents' mothers was also investigated. Authors concluded that positive effects of CBT in adolescents with CFS/ME were sustained at follow up. In addition, higher fatigue severity of the mother predicted lower treatment outcome in adolescent participants.

An RCT⁷⁰ compared 3 groups: CBT, placebo-controlled mirtazapine medication, and combined medication and CBT (n=72 participants with CFS/ME). Patients receiving CBT demonstrated significant treatment effect (measured on Fatigue Scale) at 12 weeks. By 24 weeks the group receiving CBT for 12 weeks followed by mirtazapine (tetracyclic antidepressant) for 12 weeks showed significant improvement compared to the other groups. No significant differences between treatment groups was observed for secondary measures.

An RCT⁷¹ compared family-focused CBT with psycho-education in adolescents with CFS/ME (n=63 adolescents). The results of the study showed that both therapies were effective at 6 and 12 months follow-up although those in the family-focused CBT group returned to school quicker.

10-year surveillance summary

The PACE trial (Comparison of adaptive pacing therapy [APT], CBT, GET, and specialist

medical care [SMC] for chronic fatigue syndrome) was reported and taken into account in the [review decision in 2011](#). There have since been further publications related to the trial. The following publication reported the main results. In the PACE trial⁷², 641 participants were randomly allocated to SMC alone or SMC plus CBT, GET or APT. The PACE trial aimed to assess effectiveness (fatigue and physical function) and safety (adverse events) of all 4 treatments. At 52 weeks, fatigue was significantly lower and physical function significantly higher in both CBT and GET groups compared to SMC. There were no significant differences in fatigue and physical function between SMC and APT. CBT and GET were significantly associated with less fatigue and better physical function compared with APT. Serious adverse reactions were not frequently reported and similar between the 4 groups. It was considered that the results of the study were in line with guideline recommendations on the management of CFS/ME.

A cost-effectiveness analysis of the PACE trial⁷³ reported quality adjusted life years (QALYs) and improvements in fatigue and physical function. It was concluded that comparing the 4 treatments using a health care perspective, CBT had the greatest probability of being the most cost-effective followed by GET and SMC alone. APT had the lowest probability of being the most cost-effective.

The PACE trial published data⁷⁴ on participants showing recovery from CFS/ME at 52 weeks after randomisation. Recovery was defined operationally using multiple criteria but these criteria were not presented in the abstract. Recovery was significantly more likely to happen in the CBT (32 of 143 participants recovered) and GET (32 of 143 participants recovered) groups compared to the APT (12 of 149 participants recovered) and SMC (11 of 150 participants recovered) groups.

A publication of the PACE trial⁷⁵ reported the effects of the treatments used in the trial on pain in CFS/ME. The results showed that participants reported significantly less frequent muscle pain when receiving CBT or GET compared to SMC, and when receiving GET compared to APT. Participants also reported significantly less joint pain when receiving CBT or GET compared to APT. Co-morbid fibromyalgia was significantly less frequent with GET compared to SMC.

Another publication of the PACE trial⁷⁶ reported adverse events and their association with baseline characteristics (n=641 participants). Non-serious adverse events were not significantly different between treatments. Physical function deterioration was significantly different between treatments with the lowest frequency of deterioration after CBT and the highest frequency after APT.

A pre-specified follow-up study of the PACE trial⁷⁷ assessed additional treatments received after the trial and investigated long-term outcomes (n=481 participants). Additional treatment was significantly more likely to be sought by participants originally assigned to SMC or APT compared to CBT or GET. After 2 years follow-up and compared to 1 year, improvements in fatigue and physical functioning were significant in participants originally assigned to CBT, APT and SMC but not for GET.

A planned secondary mediation analysis of the PACE trial⁷⁸ was performed (n=641 participants). The mediation analysis was used to investigate if beliefs and behaviour (as mediators) played a part in the effect that each treatment had on fatigue and physical function. The results showed that fear avoidance beliefs mediated the effect on fatigue and physical function from CBT compared to APT and from GET compared to APT. Increased exercise tolerance was a mediator of the effect on fatigue and physical function from GET compared to APT.

An RCT⁷⁹ compared an internet-based CBT treatment (Fatigue In Teenagers on the interNET [FITNET]) against usual care in adolescents with CFS/ME (n=131 participants). At 6 months, FITNET was significantly more effective than usual care for higher school attendance, absence of severe fatigue, and normal physical functioning.

An RCT⁸⁰ examined the long term efficacy of family-focused CBT compared with psycho-education in improving school attendance in adolescents with CFS/ME (n=44 participants). At 24 months follow-up, the proportion of school attendance was not significantly different between CBT and psycho-education.

An RCT⁸¹ evaluated the effectiveness of a minimal intervention based on CBT for CFS (guided self-instruction) in comparison with a waiting list (n=123 participants). After 6 months, fatigue was significantly decreased with guided self-instruction compared to waiting list.

An RCT⁸² compared CBT against a multidisciplinary rehabilitation treatment (MRT) for people with CFS/ME (n=122 participants). At 26 weeks (n=114 participants), fatigue was not significantly different between the groups. At 52 weeks, fatigue was significantly reduced with MRT compared to CBT.

An RCT⁸³ compared a group-based CBT against a waiting list in adults with CFS/ME (n=204 participants). Fatigue severity and overall impairment showed a large improvement with group-based CBT. Physical functioning and psychological distress showed a moderate improvement with group-based CBT.

An RCT⁸⁴ compared the effects on health-related quality of life (HRQL) of multidisciplinary treatment combining CBT, GET and pharmacological treatment against usual care (exercise counselling and pharmacological treatment). People with CFS/ME were included (n=120 participants). This multidisciplinary treatment did not improve HRQL and physical function and bodily pain were worsened.

The US Agency of Healthcare Research and Quality (AHRQ) report³⁸ (based on a systematic review) was evaluated by the surveillance team in October 2015 showing that

- other treatments have been inadequately studied (insufficient evidence) such as antivirals (valganciclovir) and complementary and alternative therapies (such as homeopathy, pollen extracts, and carnitine). There have been also poor reports on harms from complementary and alternative therapies. More definitive studies are needed to fill the many research gaps in diagnosing and treating CFS/ME.

The AHRQ report was updated in 2016³⁹. The purpose of the update was to assess the impact of studies using the Oxford case definition on conclusions and to assess the impact of separating studies of CBT from other counselling and behavioural interventions. A reduced strength of evidence that CBT improved function was found when studies on CBT were distinguished from other counselling therapies as well as when the Oxford case definition was used in this subgroup of CBT studies. These results suggest there is insufficient evidence that CBT improved physical function, fatigue, quality of life, and employment.

Topic expert feedback

Four editorials⁸⁵⁻⁸⁸, 6 internet communications⁸⁹⁻⁹⁴, and 2 commentaries^{95,96} were identified disputing the PACE trial, along with a critical commentary and preliminary re-analysis of the PACE trial⁹⁷ evaluating the recovery data reported by the PACE trial authors. Criticisms noted by these publications included deviations from the trial protocol when reporting the results, leading to alleged overestimates of the effect of CBT and GET.

The criticisms of the PACE trial have been addressed in editorials by the trial authors^{98,99} and in [an FAQ](#) about the PACE trial.

A report¹⁰⁰ by the ME association in 2015 was highlighted through NICE enquiries. The report provides the results of a patient survey examining acceptability, efficacy and safety of CBT, GET and pacing used as management strategies for CFS/ME. Participants were people with CFS/ME or post-viral fatigue syndrome (n=1,428 respondents) who had received 1 or more of these 3 management strategies (n=493 received CBT; n=233 received GET; n=226 received pacing). The main finding was that CBT should not be recommended as a primary intervention for CFS/ME. The report did also conclude, however, that CBT could be used if the intervention was delivered to help people with CFS/ME to learn practical coping skills and to manage comorbid conditions such as anxiety, depression and stress.

NICE was also made aware of a cross sectional survey¹⁰¹ of all 49 English NHS specialist CFS/ME adult services in 2013. Of 30 services providing a regular service to severely affected patients, 25 (83%) used CBT.

Impact statement

Through surveillance, evidence was found about different types of CBT such as CBT alone; family-focused CBT; internet-based CBT; minimal intervention based on CBT; and group-based CBT. CBT was also combined with other interventions such as biofeedback; and medication (mirtazapine). Comparison interventions included symptomatic treatment; cognitive therapy; anaerobic activity; relaxation; waiting list; usual care; routine treatment; mirtazapine; psycho-education; APT; GET; specialist medical care; and multidisciplinary rehabilitation treatment. Outcomes also varied between studies including individual strength; school attendance; self-rated symptoms;

frequency and severity of symptom deterioration; physical functioning; pain; fatigue severity; cognitive impairment; disability; social adjustment; health status; physical activity; cognitive performance; adverse events; quality adjusted life years; recovery; overall impairment; and psychological distress. Some studies did not favour CBT, for example a meta-analysis⁶⁰ showing no improvement in neuropsychological test performance in participants receiving CBT and an RCT⁸² showing reduced fatigue with multidisciplinary rehabilitation treatment compared to CBT. Another RCT⁸⁰ did not find differences between family-focused CBT and psychoeducation regarding school attendance. However, in general, most studies showed better outcomes with CBT which is aligned with current recommendations to offer CBT. No impact on the guideline recommendations is therefore anticipated.

New information has been published disputing the PACE trial which compared 4 interventions; CBT, GET, APT, and SMC. These criticisms have been responded to by the PACE authors, and none of the papers reporting on the PACE trial have been retracted. It remains that PACE is a large RCT indicating the benefits of CBT, which is aligned with current recommendations to offer CBT. If the PACE evidence was downgraded or set aside in a new systematic review, other evidence from RCTs and systematic reviews shows benefit of CBT in line with current recommendations. No impact is therefore anticipated.

An update of the AHRQ report suggests that after trials using Oxford criteria were removed from the systematic review, there is insufficient evidence that CBT improved physical function, fatigue, quality of life, and employment. Trials using Oxford criteria were eligible when developing NICE guideline CG53, and topic experts had no concerns about the inclusion criteria of trials in CFS. It was also noted by topic experts that there is no gold standard definition of chronic fatigue syndrome. There is currently insufficient consistent evidence about diagnostic methods for CFS/ME to determine an impact on the guideline recommendations.

A survey in people with CFS/ME found that although CBT was a potential intervention for learning practical coping skills and for managing comorbid conditions, the main finding was that CBT should not be recommended as a primary intervention for

CFS/ME. This result was discussed by the PACE trial authors⁹⁸ who felt that the survey findings did not negate the results of the PACE trial in showing benefits of CBT, and there were many possible reasons for the difference between the survey and the PACE results. For example, recruitment to the survey not requiring formal diagnostic assessment, lack of details/potential variability in the treatment reported on in the survey, and that surveys with an unknown sample and response rate such as this may be subject to bias. Additionally, another editorial by the PACE authors⁹⁹ discussed a different survey from 2011 by Action for ME which noted that 46% of patients had received CBT and 65% thought that it

should be made available. Limitations of survey-based evidence, and conflicting results from different surveys, limit the impact on the guideline.

CBT is offered by many English NHS specialist CFS/ME services, in line with the guideline.

The latest Cochrane review of CBT for CFS in adults was published in 2008. NICE has approached Cochrane about the possibility of updating this review.

New evidence is unlikely to change guideline recommendations.

Graded exercise therapy

3-year surveillance summary

No relevant evidence was identified.

10-year surveillance summary

A systematic review and meta-analysis¹⁰² evaluated the effects of behavioural or psychological interventions for CFS which included a graded physical activity component and examined potential moderator effects of trial characteristics (n=2,004, 16 RCTs). All outcomes at post-treatment and follow-up showed significant small to medium effect sizes with the exception of physical activity at post-treatment. The largest effects were found for fatigue severity.

The PACE trial (Comparison of APT, CBT, GET, and SMC for CFS) was reported and taken into account in the review decision in 2011. There have been further publications related to the trial. The following publication reported the main results. In the PACE trial⁷², 641 participants were randomly allocated to SMC alone or SMC plus CBT, GET or adaptive APT. The PACE trial aimed to assess effectiveness (fatigue and physical function) and safety (adverse events) of all 4 treatments. At 52 weeks, fatigue was significantly lower and physical function significantly higher in both CBT and GET groups compared to SMC. CBT and GET were significantly associated with less fatigue and better physical function compared with APT. Serious adverse reactions were not frequently reported and similar between the 4 groups. It was considered that the results of the study were in line with guideline

recommendations on the management of CFS/ME.

A cost-effectiveness analysis of the PACE trial⁷³ reported quality adjusted life years (QALYs) and improvements in fatigue and physical function. SMC patients had significantly lower healthcare costs than those receiving APT, CBT and GET. If society is willing to value a QALY at £30,000 there is a 62.7% likelihood that CBT is the most cost-effective therapy, a 26.8% likelihood that GET is most cost effective, 2.6% that APT is most cost-effective and 7.9% that SMC alone is most cost-effective.

Recovery from CFS/ME was reported after participating in the PACE trial⁷⁴ (n=585 participants). At 52 weeks after randomisation, recovery was significantly more likely to happen in the CBT and GET groups compared to the APT and SMC groups.

A publication of the PACE trial⁷⁵ reported the effects of the treatments used in the trial on pain in CFS/ME. The results showed that participants reported significantly less frequent muscle pain when receiving CBT or GET compared to SMC, and when receiving GET compared to APT. Participants also reported significantly less joint pain when receiving CBT or GET compared to APT. Co-morbid fibromyalgia was significantly less frequent with GET compared to SMC.

Another publication of the PACE trial⁷⁶ reported adverse events and their association with baseline characteristics (n=641 participants). Non-serious adverse events were not significantly different between treatments.

A pre-specified follow-up study of the PACE trial⁷⁷ assessed additional treatments received after the trial and investigated long-term outcomes (n=481 participants). Additional treatment was significantly more likely to be sought by participants originally assigned to SMC or APT compared to CBT or GET. After 2 years follow-up and compared to 1 year, improvements in fatigue and physical functioning were significant in participants originally assigned to CBT, APT and SMC but not for GET.

A planned secondary mediation analysis of the PACE trial⁷⁸ was performed (n=641 participants). The results showed that fear avoidance beliefs mediated the effect on fatigue and physical function from CBT compared to APT and from GET compared to APT. Increased exercise tolerance was a mediator of the effect on fatigue and physical function from GET compared to APT.

An RCT⁸⁴ compared the effects on health-related quality of life (HRQL) of multidisciplinary treatment combining CBT, GET and pharmacological treatment against usual care (exercise counselling and pharmacological treatment). People with CFS/ME were included (n=120 participants). This multidisciplinary treatment did not improve HRQL and physical function and bodily pain were worsen.

The US Agency of Healthcare Research and Quality (AHRQ) report³⁸ (based on a systematic review) was evaluated by the surveillance team in October 2015, which concluded that

- graded exercise therapy (GET) had broader benefit than rintatolimod but have not been adequately tested in more disabled populations (low to moderate strength of evidence)
- NICE guideline CG53 recommends GET for people with mild to moderate CFS/ME.

Cochrane reviews of exercise therapy for CFS have also been published¹⁰³⁻¹⁰⁶. The latest update of the Cochrane review from 2017¹⁰⁶ includes data from the PACE trial. Results are discussed in detail in the next section 'Exercise therapy/activity management'. The overall conclusion was patients with CFS may generally benefit and feel less fatigued following exercise therapy, and no evidence suggests that exercise therapy may worsen outcomes. The PACE data were incorporated into the Cochrane review as scores on scales

of fatigue (Chalder fatigue questionnaire) and physical function (SF-36). The direction of effect in PACE was aligned with other studies included in the Cochrane review, and a significant effect on fatigue and physical functioning was seen when including the PACE trial data in the meta-analysis.

Topic expert feedback

Four editorials⁸⁵⁻⁸⁸, 6 internet communications⁸⁹⁻⁹⁴, and 2 commentaries^{95,96} were identified disputing the PACE trial along with a critical commentary and preliminary re-analysis of the PACE trial⁹⁷ evaluating the recovery data reported by the PACE trial authors. Criticisms noted by these publications included deviations from the trial protocol when reporting the results, leading to alleged overestimates of the effect of CBT and GET.

The criticisms of the PACE trial have been addressed in editorials by the trial authors^{98,99} and in [an FAQ](#) about the PACE trial.

A report¹⁰⁰ by the ME association in 2015 was highlighted through NICE enquiries. The report provides the results of a patient survey examining acceptability, efficacy and safety of CBT, GET and pacing used as management strategies for CFS/ME. Participants were people with CFS/ME or post-viral fatigue syndrome (n=1,428 respondents) who had received 1 or more of these 3 management strategies (n=493 received CBT; n=233 received GET; n=226 received pacing). It was concluded that GET could not be seen as safe and effective for the majority of people with CFS/ME and that GET should be withdrawn by NICE and NHS specialist services until reliable methods are available for determining which people could safely benefit from GET.

NICE was also made aware of a cross sectional survey¹⁰¹ of all 49 English NHS specialist CFS/ME adult services in 2013. Of 30 services providing a regular service to severely affected patients, 24 (80%) used graded activity and 13 (43%) used graded exercise therapy.

Impact statement

New evidence suggests benefits using behavioural or psychological interventions including a graded physical activity component, which is aligned with current recommendations to offer GET. No impact on guideline recommendations is therefore anticipated.

New information has been published disputing the PACE trial which compared 4 interventions; CBT, GET, APT, and SMC. These criticisms have been responded to by the PACE authors, and none of the papers reporting on the PACE trial have been retracted. It remains that PACE is a large RCT indicating the benefits of GET, which is aligned with current recommendations to offer GET. If the PACE evidence was downgraded or set aside in a new systematic review, other evidence from RCTs and systematic reviews shows benefit of GET in line with current recommendations. No impact is therefore anticipated.

A survey in people with CFS/ME showed that GET could not be seen as safe and effective for the majority of people with CFS/ME. This result was discussed by the PACE trial authors⁹⁸ who felt that the survey findings did not negate the results of the PACE trial in showing benefits of GET, and there were many

possible reasons for the difference between the survey and the PACE results. For example, recruitment to the survey not requiring formal diagnostic assessment, lack of details/potential variability in the treatment reported on in the survey, and that surveys with an unknown sample and response rate such as this may be subject to bias. Additionally, another editorial by the PACE authors⁹⁹ discussed a different survey from 2011 by Action for ME which noted that 31% of patients had received GET and 48% thought that it should be made available. Limitations of survey-based evidence, and conflicting results from different surveys, limit the impact on the guideline.

Some form of graded activity is offered by many English NHS specialist CFS/ME services, in line with the guideline.

New evidence is unlikely to impact on the guideline.

Exercise therapy/activity management

3-year surveillance summary

A Cochrane review of 5 RCTs¹⁰³ evaluated the relative effectiveness of exercise therapy and control treatments for CFS/ME. The results suggested that some patients may benefit from exercise therapy and no evidence that exercise therapy may worsen outcomes.

A feasibility RCT¹⁰⁷ investigated the efficacy of home orthostatic training for neurally mediated hypotension (also known as fainting or syncope) in CFS/ME participants (n=38 participants). A trend towards improved fatigue was found although additional adequately powered trials are necessary.

A comparative study¹⁰⁸ compared cardiopulmonary adaptation to exercise in CFS/ME participants and a control group of healthy but sedentary women (n=85 and n=15 participants, respectively). The authors concluded that the CFS/ME group had lower work capacity in arm and leg exercises.

A comparative study¹⁰⁹ investigated the effect of exercise in CFS/ME (n=9 women with CFS/ME, n=9 healthy women). The results demonstrated a worsening of physical symptoms in participants with CFS/ME following exercise but no change in

psychological symptoms or cognitive functioning.

An RCT¹¹⁰ compared a home-delivered, nurse-led pragmatic rehabilitation programme gradually increasing activity and supportive listening against general practitioner treatment as usual (n=296 adults with CFS/ME). This was the Fatigue Intervention by Nurses Evaluation (FINE) trial. The results showed no statistically significant improvements in fatigue and physical functioning at 1 year follow-up.

10-year surveillance summary

A qualitative study¹¹¹ explored people's experience of physical activity for CFS (n=10 participants). Participants' perception of physical activity was determined on specific preconditions. Participants enjoyed physical activity when it was flexible and individually adapted. Participants felt loss of control and betrayal from their bodies if non-customised activity caused set-backs. It was concluded that personal preferences and activity levels should be used to develop exercise programmes for people with CFS/ME.

A Cochrane review of exercise therapy for CFS published in 2004¹⁰³ was updated in 2015¹⁰⁴ when NICE guideline CG53 was on the static list. It was concluded that the results of the Cochrane review were consistent with the

conclusions of NICE guideline CG53. It was decided that the guideline should remain on the static list.

The Cochrane review¹⁰⁵ was updated again in 2016. In the update, external feedback and author's response were incorporated. The Cochrane review examined the effects of exercise therapy (alone or in combination with other therapies) compared to other interventions or control for CFS/ME (n=1,518 participants, 8 RCTs). Exercise therapy was compared with 'passive' control (for example: treatment as usual, relaxation, flexibility) in 8 RCTs (n=971 participants) showing a significant reduction of fatigue after exercise therapy from 7 studies (n=840 participants) with different fatigue scales and scoring systems. One RCT reported no significant differences in serious adverse reactions between exercise therapy and 'passive' control (n= 319 participants, 1 study). Exercise therapy significantly improved sleep (n=323 participants, 2 studies), physical functioning (n=725 participants, 5 studies) and self-perceived changes in overall health compared to 'passive' controls (n=489 participants, 4 studies). Exercise therapy and CBT were compared in 2 RCTs (n=351 participants) showing no significant differences in fatigue between groups. Serious adverse reactions were not significantly different between groups.

The Cochrane review was updated again in 2017¹⁰⁶ but no further studies were added and conclusions were unchanged from the 2016 update.

A randomised crossover study¹¹² examined the differences in typical exacerbation of symptoms after high-intensity interval training (HIIT) or continuous (CONT) aerobic exercise in adults with CFS/ME (n=14 participants). The HIIT group had significantly higher mean heart rate (HR) and rated perceived exertion (RPE) in the legs compared to the CONT group. Increased fatigue was not significantly different between HIIT and CONT groups.

A study¹¹³ examined potential moderators of response to pragmatic rehabilitation compared to general practitioner treatment as usual in people with CFS/ME participating in the FINE trial. Higher levels of depressive symptoms at baseline were significantly associated with smaller improvements in fatigue in participants receiving pragmatic rehabilitation compared to participants receiving treatment as usual. From

the FINE trial, another study¹¹⁴ examined potential mediators of the effect of pragmatic rehabilitation on improvements in fatigue in the RCT participants (n=195 participants). Reduction in limiting activities and in catastrophising at 20 weeks significantly mediated the positive effect of pragmatic rehabilitation on fatigue at 20 weeks. It was concluded that changes in behavioural responses and beliefs about fatigue seemed to mediate the improvement in fatigue after pragmatic rehabilitation.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

Through surveillance, evidence was found about exercise therapy or activity management including interventions on orthostatic (Tilt)-training; high-intensity interval training; continuous aerobic exercise; and home-delivered, nurse-led pragmatic rehabilitation programme and supportive listening. Outcomes included fatigue; physical symptoms; psychological symptoms; cognitive functioning; serious adverse reactions; and overall health. Cochrane reviews show benefits of exercise therapy on fatigue, sleep and overall health. An RCT¹¹² found no differences in fatigue between high-intensity interval training and continuous aerobic exercise. A comparative study¹⁰⁹ reported worsening of physical symptoms after exercise. An RCT reported that home-delivered, nurse-led pragmatic rehabilitation programme and supportive listening was not better than general practitioner treatment as usual for fatigue and physical functioning in people with CFS/ME. Finally, a qualitative study concluded that personal preferences and activity levels should be used to develop exercise programmes for people with CFS/ME. Although evidence from systematic reviews showed benefits with exercise therapy, it was unclear whether exercise therapy was delivered with a goal-oriented and person-centred approach tailored to the needs of people with CFS/ME as suggested by the guideline. As such, the new evidence is unlikely to affect current recommendations on activity management which state to use a goal-oriented and person-centred approach tailored to the needs of the person with CFS/ME.

New evidence is unlikely to impact on the guideline.

Pacing

3-year surveillance summary

An RCT¹¹⁵ examined whether pain physiology education was capable of changing pain cognitions in participants with CFS/ME (n=48 participants). Interventions included 1 individual pain education session or 1 pacing and self-management education session (control). The pain physiology session was found to improve understanding of pain but it is not clear how this affected symptoms.

10-year surveillance summary

An RCT¹¹⁶ evaluated the effectiveness of an activity pacing self-management (APSM) intervention to improve daily life activities in women with CFS compared to relaxation (n=33 participants). There were significant changes over time in scores of the Canadian Occupational Performance Measure in both groups. Satisfaction was significantly higher with APSM compared to relaxation. The scores of the Checklist Individual Strength (which measured fatigue) significantly decreased only with APSM. The authors concluded that APSM might be feasible and effective in optimising daily life activities.

The PACE trial (Comparison of APT, CBT, GET, and SMC for CFS) was reported and taken into account in the review decision in 2011. There have been further publications related to the trial. The following publication reported the main results. In the PACE trial⁷², 641 participants were randomly allocated to SMC alone or SMC plus CBT, GET or APT. The PACE trial aimed to assess effectiveness (fatigue and physical function) and safety (adverse events) of all 4 treatments. At 52 weeks, fatigue was significantly lower and physical function significantly higher in both CBT and GET groups compared to SMC. There were no significant differences in fatigue and physical function between SMC and APT. CBT and GET were significantly associated with less fatigue and better physical function compared with APT. Serious adverse reactions were not frequently reported and similar between the 4 groups. It was considered following the surveillance in 2011 that the results of the

study were in line with guideline recommendations on the management of CFS/ME.

A cost-effectiveness analysis of the PACE trial⁷³ reported quality adjusted life years (QALYs) and improvements in fatigue and physical function. The likelihood for the most cost-effective therapy was similar from either a QALY at 30,000 and a societal perspective with the highest likelihood for CBT and the lowest likelihood for APT. Compared to SMC alone, the highest incremental healthcare cost per QALY was for APT and the lowest for CBT.

Recovery from CFS/ME was reported after participating in the PACE trial⁷⁴ (n=585 participants). At 52 weeks after randomisation, recovery was significantly more likely to happen in the CBT and GET groups compared to the APT and SMC groups.

A publication of the PACE trial⁷⁵ reported the effects of the treatments used in the trial on pain in CFS/ME. The results showed that participants reported significantly less frequent muscle pain when receiving GET compared to APT. Participants also reported significantly less joint pain when receiving CBT or GET compared to APT.

Another publication of the PACE trial⁷⁶ reported adverse events and their association with baseline characteristics (n=641 participants). Non-serious adverse events were not significantly different between treatments. Physical function deterioration was significantly different between treatments with the lowest frequency of deterioration after CBT and the highest frequency after APT.

A pre-specified follow-up study of the PACE trial⁷⁷ assessed additional treatments received after the trial and investigated long-term outcomes (n=481 participants). Additional treatment was significantly more likely to be sought by participants originally assigned to SMC or APT compared to CBT or GET. After 2 years follow-up and compared to 1 year, improvements in fatigue and physical functioning were significant in participants originally assigned to CBT, APT and SMC but not for GET.

A planned secondary mediation analysis of the PACE trial⁷⁸ was performed (n=641 participants). The results showed that fear avoidance beliefs mediated the effect on fatigue and physical function from CBT compared to APT and from GET compared to APT. Increased exercise tolerance was a mediator of the effect on fatigue and physical function from GET compared to APT.

Topic expert feedback

Four editorials⁸⁵⁻⁸⁸, 6 internet communications⁸⁹⁻⁹⁴, and 2 commentaries^{95,96} were identified disputing the PACE trial. A reply from the trial authors⁹⁸ was also found. The disputes of the PACE trial referred to the following problems with the data reported by the authors of the PACE trial:

- unjustified assumptions of random missing data
- introduction of covariates for statistical control without adequate rationale
- crossover between treatments during follow-up which was not planned in the published protocol
- report of outcome data referring to initial randomisation without reflecting the crossover between treatments during follow-up
- trial authors did not follow the protocol when they first published the main results of the PACE trial

A report¹⁰⁰ by the ME association in 2015 was highlighted through NICE enquiries. The report provides the results of a patient survey examining acceptability, efficacy and safety of

CBT, GET and pacing used as management strategies for CFS/ME. Participants were people with CFS/ME or post-viral fatigue syndrome (n=1,428 respondents) who had received 1 or more of these 3 management strategies (n=493 received CBT; n=233 received GET; n=226 received pacing). Pacing was considered to be the most effective, safe, acceptable and preferred form of activity management for people with CFS/ME.

Impact statement

Through surveillance, new evidence from an RCT concluded that activity pacing self-management might be feasible and effective in optimising daily life activities. Findings from the PACE trial showed that fatigue, physical function, recovery and pain were improved with CBT and GET compared to APT. Although the PACE trial did not find any benefits with pacing, new information has been published disputing the PACE trial showing that there were deviations from the trial protocol when reporting the results and that the corrected results of improvement in CFS/ME outcomes after CBT and GET were lower. The results of a survey showed that pacing was seen as the most effective, safe, acceptable and preferred form of activity management for people with CFS/ME. However, it was considered that new evidence from RCTs is still insufficient to recommend pacing for the management of CFS/ME.

New evidence is unlikely to impact on the guideline.

Relaxation

3-year surveillance summary

A pilot RCT¹¹⁷ investigated breathing retraining for CFS/ME participants (n=20 participants). This preliminary study indicated that breathing retraining might be useful in CFS/ME patients presenting with an asynchronous breathing pattern.

10-year surveillance summary

No relevant evidence was identified.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

During the 3-year surveillance review, evidence was found about an intervention on breathing retraining which could be useful in CFS/ME patients presenting with an asynchronous breathing pattern. It was considered that this evidence is in line with current guideline which already recommends offering relaxation techniques appropriate to the person with CFS/ME.

New evidence is unlikely to impact on the guideline.

Pharmacological interventions

3-year surveillance summary

A systematic review of controlled trials¹¹⁸ concluded that pharmacotherapy cannot be considered as first-line treatment in CFS/ME and should always be used in a context of self-management and rehabilitation.

10-year surveillance summary

An RCT¹¹⁹ evaluated the use of anti-CD20 antibody rituximab intravenous infusion for the treatment of CFS/ME (n=30 participants with CFS/ME). Fatigue was significantly improved with rituximab compared to placebo. There was a significant interaction between time and intervention group showing differences between rituximab and placebo between 6 to 10 months after intervention. Note, rituximab injections ([intravenous](#) or [subcutaneous](#)) licensed in the UK do not have a product licence for use in CFS/ME or for use in children or adolescents.

An RCT¹²⁰ examined the efficacy and safety of TLR-3 agonist rintatolimod in people with debilitating CFS/ME (n=234 participants). After 40 weeks, intra-patient placebo-adjusted exercise tolerance was significantly improved with rintatolimod. Note rintatolimod is not currently licensed for use in the UK. It was licensed in 2016 for severe CFS/ME in Argentina (see link [here](#)).

An RCT¹²¹ assessed the efficacy of lisdexamfetamine dimesylate (LDX) for the treatment of executive functioning deficits in adults with CFS/ME (n=26 participants). The Behaviour Rating Inventory of Executive Function-Adult score was significantly improved with LDX compared to placebo. Note lisdexamfetamine dimesylate is currently only licensed for use in attention deficit/hyperactivity disorder in the UK (in people aged 6 years or over).

An RCT¹²² examined the effects of oral valganciclovir compared to placebo in 30 people with CFS/ME and elevated IgG antibody titers against human herpesvirus 6 (HHV-6) and Epstein-Barr virus (EBV). Significant differences in trajectories between groups were observed in mental fatigue, fatigue severity, and cognitive function. Participants taking valganciclovir were significantly more likely to be classified as responders. Note valganciclovir is licensed in the UK, but not for CFS/ME.

An RCT reported by 2 publications^{123,124} evaluated the use of clonidine hydrochloride for CFS/ME (n=120 adolescents aged 12 to 18 years). During intervention¹²⁴, plasma norepinephrine level and serum C-reactive protein concentration were significantly lower with clonidine compared to placebo. The number of steps per day were not significantly different between clonidine and placebo groups. At 8 weeks¹²³, the clonidine group had significantly lower plasma norepinephrine and urine norepinephrine/creatinine ratio. During supine rest, the clonidine group had significantly higher heart rate variability in the low-frequency range and significantly higher standard deviation of all RR-intervals (time elapsing between 2 consecutive R waves in an electrocardiogram) compared to placebo. It was concluded that low-dose clonidine reduced catecholamine levels with sparse effects on autonomic cardiovascular control. Note clonidine is licensed in the UK, but not for CFS/ME or for use in children or adolescents.

An RCT¹²⁵ assessed the efficacy and safety of duloxetine in people with CFS/ME (n=60 participants). There were no significant differences between duloxetine and placebo for the primary outcome of general fatigue. Note duloxetine is licensed in the UK but not for CFS/ME or for use in children.

A systematic review¹²⁶ examined the existing evidence on the efficacy of drug therapies and their suitability to treat CFS/ME (26 studies). The findings showed that 10 medications were significantly effective for CFS/ME outcomes such as fatigue, pain, mood, neurocognitive dysfunction and sleep quality, symptom severity, functional status, and well-being or overall health status. However the list of medications were not reported in the abstract.

The Agency of Healthcare Research and Quality (AHRQ) report³⁸ (report from the US) was evaluated by the surveillance team in October 2015 showing that

- rintatolimod improves exercise performance in some patients (low strength evidence)
- other treatments have been inadequately studied (insufficient evidence) such as antivirals (valganciclovir) and complementary and alternative therapies (such as homeopathy, pollen extracts, and carnitine). There have been also poor reports on harms from complementary and alternative therapies. More definitive studies

are needed to fill the many research gaps in diagnosing and treating CFS/ME.

- rintatolimod has been granted orphan designation (EU/3/15/1480) for the treatment of Ebola virus disease but has no license for the treatment of CFS/ME and would not usually be considered in a clinical guideline.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

Through surveillance, inconclusive evidence was found on pharmacological interventions for

CFS/ME. Small RCTs found improvements in CFS/ME with rituximab, rintatolimod, and valganciclovir. Other RCTs found no differences between placebo and clonidine hydrochloride or duloxetine for the management of CFS/ME. The guideline currently states that there is no known pharmacological treatment or cure for CFS/ME. Further consistent evidence showing a benefit of pharmacological treatments for CFS/ME are needed before considering an update of this recommendation.

New evidence is unlikely to impact on the guideline.

Dietary interventions

3-year surveillance summary

A cross-sectional study¹²⁷ (n=51 participants) found little correlation between nutrient intake and biomarkers for CFS/ME.

An RCT¹²⁸ evaluated the efficacy of dietary interventions (low sugar low yeast compared to healthy eating) on fatigue and quality of life (n=52 participants with CFS/ME). No statistically significant differences were found in fatigue or quality of life.

A retrospective study¹²⁹ concluded that the data obtained supported the recommendation in the NICE guideline that all patients with moderate to severe CFS/ME should be encouraged to eat foods high in vitamin D.

A cross-sectional study¹³⁰ found no relationship between lifestyle factors and fatigue severity and functional impairments of CFS/ME (n=247 participants).

An RCT¹³¹ investigated the effect of aclydine, a food supplement, in the treatment of CFS/ME (n=22 adults with CFS/ME, n=22 healthy adults). The results of the study demonstrated no benefit of aclydine over placebo in treatment of CFS/ME in terms of fatigue severity, functional impairment, and biologically active insulin-like growth factor.

10-year surveillance summary

A randomised crossover study¹³² compared a high cocoa liquor/polyphenol rich chocolate (HCL/PR) against a simulated iso-calorific chocolate (cocoa liquor free/low polyphenols [CLF/LP]) in people with CFS/ME (n=10 participants). After 8 weeks, fatigue and

residual function improved significantly with HCL/PR group and deteriorated significantly with CLF/LP.

An RCT¹³³ evaluated a high-dose intermittent oral vitamin D3 therapy in adults with CFS/ME (n=50 participants). The main outcome arterial stiffness was measured using carotid-femoral pulse wave velocity showing no effect at all after treatment with vitamin D3 for 6 months.

Topic expert feedback

Topic expert highlighted that patients are not informed of the success of personalised biochemical treatment or drug interventions and referred to the Yasko protocol which includes supplements like vitamins.

Impact statement

During the 3-year surveillance review, it was concluded that evidence on dietary interventions was not likely to affect the guideline which already recommends a well-balanced diet for people with CFS/ME. During the 10-year surveillance review dietary interventions were no better than placebo/waiting list/usual care such as aclydine (food supplement) and oral vitamin D3 therapy. A positive effect was found with high cocoa liquor/polyphenol rich chocolate but the RCT was small. Through surveillance, evidence was considered to be insufficient to recommend the use of dietary interventions for the management of CFS/ME.

New evidence is unlikely to impact on the guideline.

Strategies that should not be used for CFS/ME

3-year surveillance summary

No relevant evidence was identified.

10-year surveillance summary

No relevant evidence was identified.

Topic expert feedback

Topic experts highlighted that 'over exertion pushes ME patients into an adrenaline cycle and is dangerous considering the cardiac, metabolite, impaired mitochondrial function and oxidative stress that is present.'

Impact statement

It was concluded topic experts' comments were not likely to affect the guideline which already recommends that vigorous exercise should not be offered to people with CFS/ME because this may worsen symptoms (see [recommendation 1.4.6.2](#)).

New evidence is unlikely to impact on the guideline.

Complementary and supplementary therapies

3-year surveillance summary

An RCT¹³⁴ evaluated the effectiveness of distant healing (a form of spiritual healing) for participants with CFS/ME (n=409 participants). No statistically significant effect on mental and physical health was identified.

A systematic review¹³⁵ assessed the effectiveness of traditional Chinese medicinal herbs for the treatment of idiopathic chronic fatigue and CFS/ME. No studies that met the inclusion criteria for the review were identified and as such the authors were unable to draw conclusions about the effectiveness of these products in treating CFS/ME.

A study¹³⁶ investigated intelligent-turtle massage as a treatment for people with CFS/ME (n=182 participants). This type of massage was found to be of some benefit in relieving the physical symptoms of CFS/ME.

A systematic review of 70 RCTs¹³⁷ investigated the use of alternative and complementary medicine for the treatment of CFS/ME. The authors concluded that due to the small body of evidence and the poor reporting of methodological quality no firm conclusions could be made at this time. However, the following therapies had the potential for future clinical research: acupuncture; several types of meditative practice; magnesium; l-carnitine; and S-adenosylmethionine.

A sub-study of the PACE trial¹³⁸ described the use of complementary and alternative medicine (CAM) in the trial population and its correlation with fatigue (n=640 participants). CAM use at

baseline was significantly associated with increased physical function but this increase did not reach the threshold for a clinically important difference.

10-year surveillance summary

An RCT¹³⁹ compared the effect of a 4-month qigong intervention program compared to a waitlist in people with CFS/ME (n=64 participants). Fatigue symptoms and mental functioning were significantly improved with qigong compared to waitlist.

Two RCTs^{140,141} investigated the effects of Baduanjin Qigong exercise on fatigue, anxiety, and depressive symptoms in people with CFS/ME (n=137 participants, 1 study) as well as on adiponectin evaluating whether adiponectin was involved in the anti-depressive effects of Qigong exercise on CFS/ME (n=108 women with CFS/ME, 1 study). The results of 1 of the studies showed that Qigong exercise significantly improved scores on total fatigue, physical and mental fatigue as well as depression compared to the waitlist group. The other study showed that plasma adiponectin levels were significantly raised in the group receiving Qigong exercise compared to the waitlist group. The increase in adiponectin levels following Qigong exercise were significantly associated with decreased depression.

An RCT¹⁴² examined the efficacy of acupuncture for CFS/ME (n=99 participants). The results showed larger effects in the sham acupuncture group (control group) compared to the group receiving acupuncture (intervention group) for decrease in physical and mental

fatigue as well as improvement in the physical component of health-related quality of life.

An RCT¹⁴³ compared conventional pharmacotherapy (control group) against conventional therapy together with isometric yoga (intervention group) in people with CFS/ME (n=30 participants). Fatigue decreased significantly in the yoga group but not in the control group.

An RCT^{144,145} evaluated the benefits of oral coenzyme Q10 (CoQ10) plus nicotinamide adenine dinucleotide hydride (NAHD) supplementation on maximum heart rate (max HR) during a cycle ergometer test, fatigue and biochemical parameters (n=80 participants with CFS/ME). There was a significant reduction in max HR in the intervention group at week 8 compared to baseline. Fatigue was significantly improved with the supplementation compared to placebo. There was a significant recovery of the biochemical parameters: nicotinamide adenine dinucleotide (NAD)+/NADH, CoQ10, adenosine triphosphate (ATP), citrate synthase, and lipoperoxides.

A systematic review and meta-analysis¹⁴⁶ assessed the effectiveness of body awareness interventions (BAI) in fibromyalgia (FM) and CFS/ME (29 RCTs). The results showed that BAI had significant positive effects on fibromyalgia, pain, depression, anxiety, and health related quality of life compared with control interventions. However, there was high heterogeneity for fibromyalgia and pain. The heterogeneity for anxiety, depression, and health related quality of life was from low to moderate.

An RCT¹⁴⁷ compared 6 groups receiving traditional Chinese medicine for CFS/ME:

- Lixujieyu recipe combined with Gong-Tune (group 1),
- Lixujieyu recipe combined with Jiao-Tune (group 2),
- Lixujieyu recipe combined with Yu-Tune (group 3),
- Lixujieyu recipe combined with Shang-Tune (group 4),
- Lixuiieyu recipe combined with Zhi-Tune (group 5),
- Lixujieyu recipe (control group).

Symptoms of physical fatigue related to anxiety and depression were significantly improved in groups 1 and 2 compared to control group.

An RCT¹⁴⁸ evaluated the effects of oral guanidinoacetic acid (GAA) in women with CFS/ME (n=21 participants). After 3 months, muscular creatine levels were significantly increased with GAA compared to placebo. Muscular strength and aerobic power were also significantly greater with GAA compared to placebo.

An RCT¹⁴⁹ examined the effectiveness and safety of subcutaneous injection of the human placental extract (HPE) in people with chronic fatigue including CFS/ME and idiopathic chronic fatigue (n=78 participants). In the CFS/ME group, fatigue decreased significantly with HPE compared to placebo.

An RCT¹⁵⁰ evaluated the effectiveness of a group-based self-management programme for adults with CFS/ME (n=137 participants). At 6 months, fatigue severity was significantly better with usual care compared to self-management. Self-efficacy was significantly better with self-management compared to usual care.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

Through surveillance, evidence suggested a positive effect on CFS/ME with the following complementary/supplementary therapies: intelligent-turtle massage; qigong exercise; isometric yoga; oral coenzyme Q10 plus nicotinamide adenine dinucleotide hydride supplementation; body awareness interventions; traditional Chinese medicine; oral guanidinoacetic acid and subcutaneous injection of the human placental extract. Other therapies were no better than placebo/waiting list/usual care such as distant healing (a form of spiritual healing); acupuncture; group-based self-management programme. Although there was evidence of positive effects on CFS/ME from complementary/supplementary therapies, this evidence was from single small RCTs. Therefore, there was insufficient evidence identified during guideline development to recommend the use of complementary therapies and the evidence identified through surveillance suggests that the evidence base in this area remains inconsistent.

New evidence is unlikely to impact on the guideline.

Referral to specialist CFS/ME care

3-year surveillance summary

No relevant evidence was identified.

10-year surveillance summary

A qualitative study¹⁵¹ explored hopes and expectations of people newly referred to a CFS/ME specialist service in the South of England (n=20 participants). There seemed to be a high level of uncertainty about the nature of CFS/ME from participants. Specialist service was viewed as a place where diagnosis would be clarified and guidance and support would be given.

A qualitative study¹⁵² nested within a feasibility study of interventions for CFS/ME (Specialist Medical Intervention and Lightning Evaluation [SMILE]) explored adolescents and mothers value of being referred to a specialist service for young people with CFS/ME (n=13 mothers and n=12 adolescents). Mothers and adolescents felt that the specialist service was

useful but some adolescents did not like to be limited in their activity which was part of the treatment approach.

Topic expert feedback

Topic experts highlighted the qualitative study on the SMILE trial which reports on the experience of service users (patients and parents/carers) for children with CFS/ME.

Impact statement

During the 10-year surveillance review, qualitative studies showed that people with CFS/ME positively valued referral to specialist CFS/ME services. Evidence is in line with current recommendations in that the guideline recommends a joint decision is made between the person with CFS/ME and the healthcare professional regarding referral to specialist CFS/ME care.

New evidence is unlikely to impact on the guideline.

Q – 06 Review and ongoing management

Recommendations derived from this question

- 1.8.1.1 Regular, structured review should be undertaken for all people with CFS/ME. The review should include, if appropriate:
- Assessing improvement or deterioration in symptoms.
 - Assessing any adverse or unwanted effects of therapy.
 - Ongoing investigations.
 - Considering the need to repeat investigations (for children and young people, repeating investigations should be considered if there is no improvement after 1 year).
 - Reviewing the diagnosis, especially if signs and symptoms change (see recommendation [1.2.1.4](#)).
 - Considering referral to specialist CFS/ME care.
 - Reviewing equipment needs.
 - Assessing any additional support needs (see sections [1.1](#) and [1.4](#)).
- 1.8.1.2 The timing of the reviews should depend on the severity and complexity of symptoms, the effectiveness of any interventions, and the needs of the person with CFS/ME.

Surveillance decision

This review question should not be updated.

Assessment of improvement (recovery)

3-year surveillance summary

No relevant evidence was identified.

10-year surveillance summary

A systematic review¹⁵³ examined, compared and evaluated definitions of recovery reported in the CFS/ME literature and made recommendations about the scope of recovery assessments (22 studies). The included studies showed that recovery was operationally defined by 1 or more of 5 domains:

- pre-morbid functioning
- both fatigue and function
- fatigue (or related symptoms) alone
- function alone
- brief global assessment.

The authors recommended a consistent definition for recovery capturing a broad-based return to health including assessments of fatigue, function, and people's perceptions of their recovery status.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

During surveillance, a systematic review recommended assessing fatigue, function and people's perception of their recovery status as part of a definition of recovery. It was considered appropriate to wait for more evidence before adding a definition of recovery to the guideline.

New evidence is unlikely to impact on the guideline.

Q – 07 [Key principles of care for people with severe CFS/ME](#)

Recommendations derived from this question

General principles of care

- 1.9.1.1 Management of severe CFS/ME is difficult and complex and healthcare professionals should recognise that specialist expertise is needed when planning and providing care for people with severe CFS/ME.
- 1.9.1.2 Diagnosis, investigations, management and follow-up care for people with severe CFS/ME should be supervised or supported by a specialist in CFS/ME.
- 1.9.1.3 People with severe CFS/ME may need to use community services at times. These services may include nursing, occupational therapy, dietetics, respite care, psychology and physiotherapy (see the 'National service framework for long-term conditions*'). The input of different professionals should be coordinated by a named professional.
- 1.9.1.4 People with severe CFS/ME should be offered a summary record of every consultation because of their cognitive difficulties.
- 1.9.1.5 Most people with CFS/ME will not need hospital admission. However, there may be circumstances when a planned admission should be considered. The decision to admit should be made with the person with CFS/ME and their family, and be based on an informed consideration of the benefits and disadvantages. For example, a planned admission may be useful if assessment of a management plan and investigations would require frequent visits to the hospital.

Rest

- 1.9.2.1 When making decisions about prolonged bed rest, healthcare professionals should seek advice from a specialist experienced in the care of people with severe CFS/ME. The significant physical and psychological risks associated with prolonged bed rest should be taken into account.

- 1.9.2.2 Healthcare professionals working with people with severe CFS/ME who are in bed most (or all) of the time, should explain the associated risks (such as postural hypotension, deep venous thrombosis, osteoporosis, pressure sores and deconditioning) and monitor these.

Management approaches

- 1.9.3.1 People with severe CFS/ME should be offered an individually tailored activity management programme (see recommendation [1.6.2.22](#)) as the core therapeutic strategy, which may:
- be delivered at home, or using telephone or email if appropriate
 - incorporate the elements of recommendation [1.6.2.22](#) and draw on the principles of CBT and GET (see recommendations [1.6.2.1–21](#)).
- 1.9.3.2 An activity management programme should be reviewed regularly and frequently.

* Available from the [Department of Health](#).

Surveillance decision

This review question should not be updated.

Self-management

3-year surveillance summary

No relevant evidence was identified.

10-year surveillance summary

An RCT¹⁵⁴ assessed the efficacy of fatigue self-management for severe CFS/ME (n=137 participants with severe CFS/ME) comparing 3 interventions: fatigue self-management with web diaries and actigraphs (FSM:ACT); fatigue self-management with less expensive paper diaries and pedometers (FSM:CTR); or usual care control condition (UC). At 3-month follow-up, fatigue severity was significantly reduced with FSM:CTR and with the combination of active treatments compared to UC but not at 12-month follow-up.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

During surveillance review, evidence showed that long-term fatigue improvement was not sustained with self-management interventions. It was considered that evidence was not likely to affect current recommendations for the management of severe CFS/ME because self-management interventions are not part of the interventions for the management of severe CFS/ME.

New evidence is unlikely to impact on the guideline.

Prognosis

3-year surveillance summary

No relevant evidence was identified.

10-year surveillance summary

No relevant evidence was identified.

Topic expert feedback

A retrospective cohort study¹⁵⁵ investigated mortality in people with CFS/ME (n=2,147 cases were identified). In a period of 7 years, 17 deaths were found. There were no significant differences in age-standardised and sex-standardised mortality ratios for all-cause mortality or cancer-specific mortality in people with CFS/ME compared with the general

population in England and Wales. A significant increase in suicide-specific mortality was found. It was concluded that suicidality should be assessed in people with CFS/ME.

Impact statement

During surveillance, evidence suggested an increase in suicide-specific mortality in people with CFS/ME. The guideline already recommends to treat any comorbid mood disorder according to NICE clinical guidelines. Therefore, this evidence was not considered to affect current recommendations.

New evidence is unlikely to impact on the guideline.

Research recommendations

RR – 01 Are intervention strategies that have been shown to be effective in mildly to moderately affected adults also effective in children and in people (adults and children) with severe CFS/ME?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered during the update of the guideline.

RR – 02 Are there more efficient ways of delivering standard methods of care? For example, what is the most efficient way of delivering domiciliary care for people with CFS/ME?

[New evidence](#) relevant to the research recommendation was found partially addressing the RR.

The evidence shows that a home delivered pragmatic rehabilitation programme and supportive listening (nurse-led intervention) was not better than general practitioner treatment as usual for fatigue and physical functioning in people with CFS/ME.

Surveillance decision

This research recommendation will be considered during the update of the guideline.

RR – 03 What is the prevalence and incidence of CFS/ME in different populations?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered during the update of the guideline.

RR – 04 What is the natural course of the illness?

[New evidence](#) relevant to the research recommendation was found partially addressing the RR.

Evidence comes from a systematic review that recommended assessing fatigue, function and people's perception of their recovery status as part of a definition of recovery.

Surveillance decision

This research recommendation will be considered during the update of the guideline.

RR – 05 What is the best way of measuring outcome in research studies?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered during the update of the guideline.

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