**Eight major errors in the review process and interpretation of the evidence in the NICE guideline for chronic fatigue syndrome and myalgic encephalomyelitis**

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**Abstract**

Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) is a disabling long-term condition of unknown cause. The National Institute of Health and Clinical Excellence (NICE) published a guideline in 2021 that highlighted the seriousness of the condition, but also recommended that graded exercise therapy (GET) should not be used and cognitive behaviour therapy (CBT) should only be used to manage symptoms and reduce distress; not to help the illness itself. This U-turn in recommendations from the previous 2007 guideline is controversial.

We suggest that the controversy stems from eight major errors of both process and interpretation of the evidence by the NICE committee. The committee: 1) Created a new definition of CFS/ME, which automatically “down-graded” the certainty of trial evidence; 2) Omitted data from standard trial end points used to assess efficacy; 3) Discounted trial data when assessing treatment harm in favour of lower quality surveys and qualitative studies; 4) Down-played the importance of fatigue as an outcome; 5) Failed to synthesise and GRADE trial evidence adequately; 6) Misrepresented GET as mandating fixed increments of change when the major trials defined it as collaborative, negotiated, and symptom dependent; 7) Deviated from NICE recommendations of rehabilitation for related conditions, such as chronic primary pain; 8) Recommended an energy management approach in the absence of supportive research evidence.

We conclude that the errors in this guideline were the result of abandoning the normal scientific standards of the NICE process, with the consequence of denying patients potentially helpful treatments and risking persistent ill health and disability.

**Introduction**

Chronic fatigue syndrome (CFS) is a disabling long-term condition, characterised by severe fatigue, and a number of other symptoms that are typically made worse by minimal physical or mental exertion (post-exertional fatigue and malaise).1 In addition to fatigue, other common symptoms include cognitive difficulties, sleep disturbance, and muscle pain.1, 2 Whilst some believe myalgic encephalomyelitis (ME) is a different condition from CFS, most authors believe they are the same illness (CFS/ME).1, 2

The United Kingdom National Institute for Health and Care Excellence (NICE) was founded in 1999. “Although NICE has authority only in England, their publications are generally seen as providing high-quality evidence-based summaries that are highly influential in shaping clinical practice world-wide.”3 NICE’s 2007 CFS/ME guideline recommended offering two specific forms of rehabilitation, namely graded exercise therapy (GET) and cognitive behaviour therapy (CBT), to those with mild or moderately severe CFS/ME.4 These recommendations were based on the evidence review that NICE itself commissioned, which concluded that: “Graded exercise therapy and cognitive behaviour therapy appeared to reduce symptoms and improve function, based on evidence from RCTs.”5

NICE published a new guideline in October 2021, which concluded that the evidence of benefit for rehabilitation in general and specifically for both CBT and GET was of low or very low certainty, using the GRADE evidence appraisal approach.6 The guideline recommended that GET should not be provided and qualified the use of CBT, which they concluded was only useful for managing symptoms and treating distress, but was not a treatment for the core illness itself.6

Such a substantial change to the previous recommendations would be understandable if in the fourteen or so years that had elapsed the balance of the evidence had fundamentally changed. But this is not the case. Indeed, an internal NICE Review in 2017 had concluded that there was no new evidence to justify a revision of the previous guideline. This was because several updated systematic reviews and meta-analyses had continued to support the use of both these treatments, with more trials published,7-11 (although one review revised its decision to support these treatments after arbitrarily excluding trials using one particular diagnostic definition).12 These reviews included the PACE trial that had a far larger sample size (n = 640) than any of its predecessors, and compared specialist medical care alone to three therapies: CBT, GET and adaptive pacing therapy, all in addition to specialist medical care.13 Almost all of the trials published since 2007, including the PACE trial, found overall benefit for both CBT and GET and those trials that examined safety outcomes found no evidence of excess treatment related harm when compared to the other interventions.10, 11, 13 Adaptive pacing therapy, which was based on the same model of “energy management” that is now recommended by the new guideline, was found to be demonstrably less effective than both GET and CBT and of no benefit compared to medical care alone.13

Yet despite the findings of these reviews, NICE decided to revise radically the 2007 guideline. This revision has met considerable opposition.14 Three clinicians working in the field resigned from the NICE committee before publication.15 Four Royal Colleges of Medicine concluded that “Graded Exercise Therapy as defined in the guidance is not reflective of the personalised paced exercise programmes that are currently used in the NHS and termed GET. These have provided benefit to many patients and should not be discontinued.”16 And: “CBT remains a valuable treatment for alleviating symptoms in CFS/ME and services should ensure patients have access to this… .”16 A Lancet commentary concluded that: “By selective use of the evidence from randomised studies, cherry-picking statements from qualitative studies, and relying on the opinions of the committee, NICE disregarded the best available research evidence and tarnished the guideline process.”17

So, what went wrong? In this article we describe some of the major errors in the evidence synthesis, appraisal and interpretation that appear to have underpinned the revised guidance.

**The uncontroversial conclusions about CFS/ME in the guideline**

Before we discuss the errors that led to the controversy, we want to make clear that there are many things known about this illness, which are agreed by all, and which were included in the guideline.6 These important agreements include the following points. CFS/ME is a debilitating condition which seriously impacts the individual’s life as well as those around them. Some patients are so disabled that they may be bed-bound or house-bound, thereby being less able to access care and treatment. Post-exertional malaise is a common and important symptom of the illness. CFS/ME does have a pathophysiology, although much of this remains to be discovered. People with CFS/ME can experience stigma, disbelief, and dismissive attitudes from health and other professionals. Any treatment should be mutually agreed and delivered collaboratively. Simply telling patients to exercise more may make them worse. Finally, even the most evidence-based treatments of CBT and GET do not help everyone.

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| **Box 1. Uncontroversial conclusions about CFS/ME in the guideline**   * CFS/ME is a serious and debilitating condition * Some patients are severely disabled, which may limit access to care and treatment * Post-exertional malaise is a common and important symptom of the illness * CFS/ME shows pathophysiological changes, but these require further research * People with CFS/ME may not have their illness taken sufficiently seriously by health and other professionals * Treatments for CFS/ME should be negotiated between healthcare professionals and patients and should always be delivered collaboratively * Simply telling patients to exercise more may make them worse * Evidenced based therapies for CFS/ME, such as CBT and GET, do not benefit all patients |

**Controversial recommendations about the management of CFS/ME in the guideline**

We suggest that the controversial recommendations about the management of CFS/ME occurred because of errors in the identification and synthesis of data for the NICE guideline. For full details of these and other criticisms of the review process, please refer to the lengthy and detailed submissions provided independently in response to the consultation on the draft guideline by four Royal Colleges of Medicine and the Association of British Neurologists, among others, which are available on the NICE Guideline website.18. 19 There was a remarkable consistency in the criticisms made by these organisations, yet the NICE committee did not adequately address the large majority of their suggestions.

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| **Box 2. The NICE committee’s eight major errors in the CFS/ME 2021 guideline process and outcome**   * Created a new definition of CFS/ME, which automatically downgraded the certainty of trial evidence * Omitted data from standard trial end points used to assess efficacy * Discounted trial data when assessing treatment harm in favour of lower quality surveys and selective comments from qualitative studies * Downplayed the importance of fatigue as an outcome, even though this is the primary symptom of CFS/ME * Failed to synthesise and GRADE trial evidence adequately * Misrepresented graded exercise therapy as mandating fixed increments of change when the major trials defined it as collaborative, negotiated, and symptom dependent * Deviated from NICE recommendations of rehabilitation for related conditions, such as chronic primary pain * Recommended an energy management approach in the absence of supportive research evidence |

**1. The creation of a new definition of CFS/ME, which automatically downgraded the certainty of trial evidence**

A new set of diagnostic criteria for CFS/ME was devised by the NICE committee creating the guideline.6 Partially based on a previous review of the evidence,1 but not guided by the Guidelines International Network eight item checklist for modifying disease definitions,20 the committee decided that a provisional diagnosis of CFS/ME should only be made if patients have all four symptoms of: debilitating fatigability, post-exertional symptom exacerbation, unrefreshing sleep and cognitive difficulties.6 (The committee preferred the term “post-exertional symptom exacerbation” to “post-exertional malaise” (PEM)). Whilst there is strong evidence that PEM is an important and common symptom of CFS/ME,1 the new guideline made it mandatory for making the diagnosis. This is problematic as PEM is not a mandatory symptom in the Centers for Disease Control and Prevention (CDC) definition which, with over 6,000 citations on Google Scholar, is far and away the most widely researched definition of the condition.21 The NICE committee then instructed the UK National Guideline Centre (NGC), which was tasked with undertaking the systematic reviews and meta-analyses, to down-grade all those trials that did not specifically and explicitly require participants to report the symptom of PEM as a mandatory criterion for recruiting participants.22 As this was a newly created definition, in one stroke the panel had down-graded nearly thirty years of research from serious consideration by the National Guideline Centre.

The emphasis NICE placed on PEM is debatable.2, 23 Its prevalence varies according to how the symptom is defined and it is not specific to CFS/ME, being found in most conditions which present with pathological fatigue.24-27 PEM is also subjective, by definition, as are all the symptoms that make up the syndrome of CFS/ME. In contrast, the guideline authors made repeated criticisms of the outcome measures used in all the trials they considered as being too “subjective” (see 4th error below), but did not apply the same tests or arguments to the equally subjective symptom of PEM itself. NICE’s own reviewers found only one study that tested the diagnostic utility of individual symptoms, which stated that PEM had a sensitivity of 0.50 and specificity of 0.57, i.e. low.22 As NICE concluded: “The [established] diagnostic criteria have not been evaluated in terms of their measurement validity and accuracy in diagnosing ME/CFS.”22 This equally applies to the newly proposed NICE diagnosis.

Most trials have used either the CDC or Oxford definitions of CFS/ME, neither of which mandated PEM, although it is an optional symptom of the CDC definition.21, 28 PEM is common in populations of patients with CFS/ME. Some 86 to 95% of participants reported PEM in eight CBT trials available for consideration, the prevalence depending on its definition (H Knoop personal communication). An individual patient data analysis found no moderating effect of PEM on the impact of CBT on either fatigue or functional outcomes (H Knoop, personal communication). In other words, the effects of CBT were similar for patients with and without PEM. NICE did not contact the trial authors for these data, even though a summary of them was submitted to NICE during the consultation period.19 NICE did undertake a sensitivity analysis to assess whether the presence of PEM in trials affected outcomes. However, they arbitrarily set the threshold for trials with the prevalence of PEM at >94% of participants, did not include trials that gathered self-reports of this symptom, and did not include the data from the eight trials mentioned above.29

Furthermore, one trial of self-help based on the principles of GET, which did use an illness definition that mandated PEM, found the exercise intervention was effective in reducing fatigue.30 Another large trial (PACE) used a sensitivity analysis to show that using an ME definition that mandated post-exertional fatigue made no significant difference to the more positive outcomes after both CBT and GET, when compared to adaptive pacing and usual care.13 Indeed, PEM improved more with both CBT and GET compared to the comparison treatments.13 Although the evidence suggests that the presence or absence of the symptom of PEM made little difference to the outcomes, the NICE committee ignored this.

In summary, adopting PEM as a mandatory symptom for trial participants was not based on robust research. The committee itself was explicit that this decision was based on their own opinions. Even after deciding to adopt PEM as a mandatory symptom, the limited evidence available to NICE suggested that it made no difference to either fatigue or physical function outcomes obtained with GET. Therefore, downgrading the certainty of evidence on this basis (of indirectness or applicability) was flawed.29, 31

**2. Omission of data from standard trial end points used to assess efficacy**

The NICE committee failed to use data from all time points and ignored predefined end-point timings of trials. To comprehensively assess treatment effects over time, meta-analyses should use all time points that directly evaluate the effect, but also note the impact of treatment crossovers with time.32 After the end of any trial, participants are free to take up any treatment they wish. Any longer term follow up is purely naturalistic and outcomes, good or bad, are progressively less attributable to the original treatment to which the participants were randomised. However, the NICE committee chose only to consider outcomes for each trial at the data point furthest away from randomisation. The justification for this decision was to allow examination of long-term outcomes, such as mortality; but since CFS/ME is not a fatal disease, this justification is unconvincing.33 The decision sometimes led to ignoring earlier trial outcomes that were assessed at times assigned *a priori* as primary end-points.31 This was the case even when participants were no longer receiving treatment to which they had been allocated in the trial and were free to undertake other treatments. Ignoring such crossovers would have diluted any effects detectable in the longer term outcomes.34 This decision had a major impact on the results of the largest trial, the PACE trial.13

Most trials only published outcomes at the predefined trial endpoint. However, although the primary outcome for the PACE trial was 12 months from randomisation, trial participants were also followed up naturalistically at 2.5 years after randomisation.34 By this time, cross-over of treatments had often occurred and 44 per cent of PACE trial participants had received either another course of the original therapy allocated or another trial therapy.34 An unknown number had additional non-trial treatments. Consequently, it was unsurprising that no significant differences in the primary outcomes (of fatigue and physical function) were observed across the original randomly allocated groups by this time.34 The overall improvement in the CBT and GET groups was maintained in the PACE trial and the patients who had initially received other interventions also improved; i.e. they caught up.34 This finding was used by NICE to conclude incorrectly that these treatments were ineffective.31 The 6 and 12 months’ findings of clear benefit for both CBT and GET, from the largest clinical trial in the literature, were simply ignored.13, 31 A cursory look at other current NICE guidelines to related or overlapping long-term conditions shows that this is not standard practice for NICE.35

**3. Discounting trial data when assessing treatment harm in favour of lower quality survey and selective comments from qualitative reports**

Harm is a critical issue to consider for all treatments, including both psychological and physical therapies. As worsening can occur due to the natural history of the condition, harms should be assessed alongside benefits by extracting data from randomised clinical trials with comparisons made across interventions, in order for the strongest inferences to be drawn. The NICE committee inverted the usual evidence hierarchy by not adequately considering the reassuring evidence of the low risk of treatment harms within randomised controlled trials, of GET in particular, and instead prioritised qualitative studies and patient organisation surveys.31 Qualitative studies cannot provide systematic evidence of safety; only randomised clinical trials and non-randomised studies of interventions can do that. Furthermore, patient organisation surveys can be criticised for neither ensuring the validity of diagnoses,36 nor clarifying whether GET was graded and individualised.37 Such surveys are also subject to selection bias.

Both the PACE trial and a more recent trial systematically examined six safety variables in all participants and found no evidence of harm after GET compared to comparison interventions.13, 30, 38 NICE were provided with a summary of a meta-analysis of further safety data from all ten published trials of GET.39 This meta-analysis found no excess evidence of harm in relation to either the number of participants withdrawing from GET or the number rating their overall health as worse after treatment, when compared to control interventions.39 The meta-analysis did find that more participants dropped out of trial follow up after GET when compared to control interventions (11% versus 7%), but the authors suggested that this might have been related to too intense initial exercise being used.39 So, whilst systematic studies of the safety of GET found no convincing evidence of harm with GET, NICE nonetheless concluded that GET was not safe. A recent consensus statement reiterated that the benefits of physical activity outweigh the risks in long-term health conditions in general.40

**4. Downplaying the importance of fatigue as an outcome, even though this is the primary symptom of CFS/ME**

The NICE committee instructed the UK National Guideline Centre to downgrade all fatigue outcomes on risk of bias on the premise that it is a subjective measure.31 This was inconsistent with the diagnosis of CFS/ME; all definitions depend on self-reported symptoms that are by definition subjective. This subjectivity holds true for all four symptoms - debilitating fatigability, post-exertional symptom exacerbation, unrefreshing sleep and cognitive difficulties - included in the new NICE diagnostic criteria of CFS/ME.6 This is analogous to downgrading the importance of pain as an outcome in treatment trials of chronic pain. At the present time there is no objective test that can tell us whether a patient has or does not have CFS/ME, so applying a different standard to outcome data from the diagnostic criteria is inconsistent and illogical

The NICE committee also decided that therapy trials not being “blinded” impaired the validity of the results.31 No attention was paid to the Medical Research Council’s framework regarding the development and evaluation of complex interventions.41 There was a failure to take expert evidence from a clinical trialist with experience in complex intervention methodology.6, 31 Had this happened, a more considered approach to the analysis of evidence would have been possible, rather than incorrectly judging it against the methodology of a drug trial. It is worth noting that a recent meta-epidemiological study of 142 Cochrane trial meta-analyses concluded that concerns over bias by lack of blinding in randomised trials may have been exaggerated.42

The guideline provided a description of what CBT entails.6 However, it suggests that CBT should focus primarily on support for managing symptoms and treating [emotional] distress, which was seen as a consequence of the illness. This is not what rehabilitative CBT was developed to achieve or how it was delivered in the trials for CFS/ME. The primary intention of CBT in this context was to help patients to reconsider their thoughts, fears and activity in order to improve their fatigue and ability to do things. Suggesting that CBT should only be used to manage symptoms and reduce distress associated with having a chronic illness implies that the “core illness” itself will not be changed.6 This is puzzling given that CFS/ME is defined purely in term of symptoms and impaired functioning. There is no such thing as asymptomatic CFS/ME. If symptoms resolve and there is a sustained return to normal life, the patient has recovered. A treatment that improves fatigue and functioning is therefore a treatment that can improve the condition, often substantially, as the trial evidence clearly shows.

# **5. Failure to synthesise and GRADE the trial evidence adequately**

The research evidence was not presented transparently by NICE, so that the decision-making process was less robust. Normal guideline development involves the research evidence being synthesised by methodological specialists, followed by the guideline development committee’s deliberations around benefits and harms being made transparently, with clear reasons for the resultant agreed recommendations.32 With complex interventions, NICE methodologists are available to characterise the components of the intervention, the theory of change, and then characterise each trial to allow groupings. This did not happen. The analysis was mainly at the level of the individual trial; there was remarkably little aggregation and meta-analysis, without adequate rationale or explanation, which resulted in lower power and increased uncertainty.31

This lack of a robust process of evidence synthesis and guideline development was remarked upon by four Royal Colleges of Medicine, which commented: “There is considerable disquiet in the medical profession and some patient groups about the way the data and evidence have been assessed…”.16 The original GRADE (Grading of Recommendations, Assessment, Development and Evaluations) methodologists were more damning, describing the review as “…a disastrous misapplication of GRADE methodology,…“43

The application of the GRADE Evidence to Decision framework fell short of international expectations.32 The committee did not consider the benefits and harms of various interventions in the light of the certainty of the evidence. Indeed, the GRADE evidence tables were so disaggregated it is hard to make sense of them.29, 31 The certainty of evidence of harms from qualitative studies should have been discounted as it is of very low certainty.

**6. Misrepresentation of graded exercise therapy as employing fixed increments of change** **when the major trials defined it as collaborative, negotiated, and symptom dependent**

NICE misrepresented graded exercise therapy (GET). The description used by NICE is different from that given in their previous 2007 guideline, and different from that used in most trials of GET.11 In the current guideline, NICE described GET as incorporating fixed increments of exercise that are pursued irrespective of how the patient feels.6 This description is at odds with the therapy reported in the published trials. Clinics, trials and the previous guideline make clear that in GET, activity is determined collaboratively with the patient and only increased as the patient feels able, dependent on their symptomatic response. The description of GET from the very first trial, published as long ago as 1997, stated: “If they [the patient] complain of fatigue in response to a new level of exercise, they should be advised to remain at the same level for an extra week, rather than progressing the duration, and to increase the exercise when the symptoms regress.”44 The PACE trial GET manual states: “If it [exercise] can’t be done every day, then the starting level is too high”, and in regard to a new level of exercise: “Keep to this level of activity until you are used to it and it feels OK. *Once it feels OK* [our italics] (you’re getting stronger!), another small increase in time can be added.”45 So, there are no “fixed increments of exercise” in GET. NICE have therefore banned a treatment that is neither described in the research evidence nor routinely given in specialist clinics. The current guideline does describe an exercise programme, for those who wish to try it, but the content of this is not that as used in trials, being more like pacing (see below), and thus lacking evidence of efficacy.6, 13

**7. Deviation from NICE recommendations of rehabilitation therapies for related conditions, such as chronic primary pain**

Although not strictly an error of process or interpretation, there is a stark contrast to other relevant NICE guidelines. NICE published a guideline for the management of chronic primary pain in 2021.35 Chronic primary pain includes disorders such as fibromyalgia, which overlap substantially with CFS/ME in terms of comorbidity and current aetiological and mechanistic thinking.46 Population-based studies show a considerable overlap between these two conditions.47 Indeed, the term ‘myalgic’ in ‘myalgic encephalomyelitis’ highlights how commonly people with CFS/ME experience pain.

Despite the strong clinical overlap, the conclusions could hardly have been more different in the primary pain guideline. For chronic primary pain, NICE recommends rehabilitation therapies, including graded exercise and psychological therapy.35 For clinicians seeing patients where CFS/ME co-exists with chronic primary pain the contrasting advice is confusing. Furthermore, NICE recommends both CBT and exercise therapies in a range of neurological conditions, such as multiple sclerosis, where it can improve both fatigue and mobility.48 Such treatments are welcomed by these patient communities and adopted into treatment pathways and recommendations. This inconsistent approach is confusing for the outside world and needs to be addressed.

NICE responded to these criticisms by suggesting that the pain in CFS/ME, which it is not disputed by any party as being very prevalent, is in fact a different kind of pain to that found in fibromyalgia – namely neuropathic pain. The guideline refers the reader to the NICE guideline on neuropathic pain.6 However, the pain of CFS/ME is unlikely to be neuropathic. Neuropathic pain is that caused by a lesion or disease involving the somatosensory nervous system.49 There is no evidence that this is the case in CFS/ME, and the International Association for the Study of Pain does not include CFS/ME as a cause of neuropathic pain.49 The category of nociplastic pain, which is equivalent to chronic primary pain, is likely to be the correct category for the pain of CFS/ME.50

**8. Recommendation of an energy management approach in the absence of supportive research evidence**

Having erroneously downgraded the randomized trials of CBT and GET as primary treatments, NICE recommended “energy management”, in which patients are encouraged to stay within the energy limits imposed by their illness, and thus avoid exacerbating symptoms.6 This approach is often described as pacing. Having rejected CBT and GET due to alleged lack of evidence, what greater evidence convinced NICE to recommend “energy management”? NICE recommended this approach based on the experience of the guideline committee, yet the research evidence suggests otherwise. The only substantial trial of pacing for CFS/ME published to date was as one arm of the PACE trial, which showed that adaptive pacing therapy, supported by an occupational therapist, was no more effective than specialist medical care alone and clearly less effective than either CBT or GET.13

**Conclusions**

The new guideline includes important and uncontroversial statements about CFS/ME. However, the treatment recommendations are tendentious. We have presented evidence that both the processes of synthesis of the evidence and decision making were distorted, leading to a misrepresentation of the research evidence, which itself led to substantial and unwarranted changes from the 2007 guidelines. It is beyond logic to start with a guideline that recommends two treatments, for which the research evidence has strengthened, not weakened, over the following decade, and end with a guideline that removes one, and qualifies the other, replacing them with “energy management”, for which there is little if any evidence.

The recent Lancet commentary on the new guideline concluded: “In our view, this guideline denies patients treatments that could help them, undermines NICE as an international authority in guideline development, and jeopardises fundamental scientific principles by allowing some processes driven by ideology.”17 We agree with this statement. We are concerned that this new guideline will effectively deny clinicians the ability to offer these treatments to those patients who want them and this risks perpetuating chronic ill health and disability. Why deny patients the choice of treatments that may help them?

What is now required is a new systematic review and meta-analysis of the relevant treatment trials, without the errors that we have described. The forthcoming individual patient data meta-analysis of exercise therapy trials for CFS/ME is a step in the right direction.51 NICE then needs to reconvene a panel with an appropriate mix of specialists, methodologists, and patients (both recovered and those still unwell), to revise the guideline, based on the new review. As well as this, there is a great need for more rigorous clinical trial research into novel interventions for those who do not respond to either CBT or GET.

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**Competing Interests**

PW was a co-author of trials of both graded exercise therapy and cognitive behaviour therapy, including the PACE trial, is a trustee of the Voluntary Hospital of St Bartholomew’s Charity, was a previous member of Independent Medical Experts Group, which advises the UK MoD on its Armed Forces Compensation Scheme, and receives personal consultancy fees from Swiss Re reinsurance company. BA was a centre leader in the PACE trial. AJC reports grants from NIHR (Physio 4 FMD) and CSO (Long Covid Cognitive phenotyping). AJC is a paid associate editor of JNNP and unpaid president elect of the Functional Neurological Disorders Society (FNDS), he gives expert testimony in court on a range of neuropsychiatric topics on a 50% claimant 50%: defender basis. He is the author of a self-help book based on CBT principles for treatment of FND (no royalties taken). DC declares grants from Pfizer and Aptinyx; consulting fees from AbbVie Inc, Allergan Sales LLC, Heron Therapeutics, Inc, Eli Lilly and Company, Aptinyx, Inc., H. Lundbeck A/S, Neumentum Inc., Pfizer, Inc, Regeneron Pharmaceuticals, Inc., Samumed, LLC, Swing Therapeutics, Inc., Tonix Pharmaceuticals, Inc., Virios Therapeutics, Inc. Fees from Fasken Martineau DuMoulin LLP, Kellogg, Hansen, Todd, Figel & Frederick, PLLC, Marks & Clerk Law LLP, Nix Patterson LLP, Pfizer, Inc, Zuber Lawler & Del Duca LLP. JAC reports consulting fees from Bial, and honoraria from Janssen, Bial, and Brittania. BAD reports NIH R13 infrastructure grant for 2022 Functional Neurological Disorders Society meeting in Boston. TC was co-investigator of several trials of behavioural interventions for CFS/ME, including the PACE trial, has received royalties for several books and book chapters on CFS/ME and received payments for workshops on CBT for CFS/ME. BAD is on the board of directors of the FNDS and receives royalties from Oxford University Press for “Psychogenic Nonepileptic Seizures: Towards the Integration of Care”. She does paid consultancy for Bioserenity (EEG interpretations) and Best Doctors (clinical consultations). She received support to attend the American Epilepsy Society Board of Directors meeting in 2021. She chairs the data safety monitoring board of the DSMB NIH-ESETT trial 2015-2019, and received travel expenses to attend the American Epilepsy Society Board of Directors FNDS meeting and Epilepsy Foundation of New England PAB. MJE reports royalties from Oxford University Press for the book “The Oxford Specialist Handbook of Movement Disorders”, consulting fees from UCB (personal) and Merz Pharma (to his institution), honoraria from the International Parkinson’s Disease and Movement Disorder Society, medicolegal fees for personal injury and clinical negligence cases, support to attend meetings from the FNDS, leadership roles in International Parkinson’s Disease and Movement Disorder Society and Dystonia UK, and is a medical board member of FND Action and FND Hope, and board member of the FNDS. JE was the President of the Faculty of Sport and Exercise Medicine at the time of the Royal College of Physicians’ review of this guideline and submitted comments on behalf of the Faculty. He is Medical Director of a company which occasionally manages patients with CFS/ME. AJE has received grant support from the NIH and the Michael J Fox Foundation, personal compensation as a consultant/scientific advisory board member for Neuroderm, Neurocrine, Amneal, Acadia, Acorda, Bexion, Kyowa Kirin, Sunovion, Supernus (formerly, USWorldMeds), Avion Pharmaceuticals, and Herantis Pharma, and publishing royalties from Lippincott Williams & Wilkins, Cambridge University Press, and Springer. He received an honorarium from Avion. He cofounded REGAIN Therapeutics (a biotech start-up developing nonaggregating peptide analogues as replacement therapies for neurodegenerative diseases) and is co-owner of a patent that covers synthetic soluble nonaggregating peptide analogues as replacement treatments in proteinopathies. PF declare consulting fees from FADL Forlag, Munksgaard, Ny Nordisk Forlag and Arnold Busk, an honorarium from Lundbeck Pharma, and medicolegal fees from Retslægerådet. SF was a co-founding member of the GRADE working group and a member of the GRADE guidance group. She has been engaged in debates related to the evidence regarding CFS/ME for many years from a biopsychosocial perspective. PG declares an NHMRC Investigator Award: “Neglected Problems in Health Care” supporting his salary; grants from the National Heart Foundation, Commonwealth Department of Health and WHO for work unconnected to this paper, and is a board member (unpaid) for Therapeutic Guidelines Limited. IH has an NRS Fellowship from CSO, has been paid for medicolegal consultations, receives travel expenses for attending medical conferences and one honorarium from Bristol NHS Neurology Department, and is on the board of Fowler’s syndrome UK Charity. WH was a member of the 2007 NICE Guideline Development Group, and is Chief Medical Officer of LV=, an insurance company. PH was part of the steering committee of the German clinical practice guideline on functional somatic symptoms. MH reports fees for medicolegal expert court reports (none concern CFS/ME). HK reports grants from ZonMw, Stichting NKCV, MS Research, and Dutch Cancer Society, was co-author of trials of cognitive behaviour therapy, reports royalties for a published treatment manual for CBT for fatigue in CFS/ME, and an honorarium for a lecture from Intercept Pharma Deutschland GmbH. A Lehn is an unpaid director of the FNDS. A Lloyd reports grants for investigator initiated research grants from Gilead Sciences, AbbVie, and Sequiris Pty Ltd. AM has been on a trial steering committee for a trial of graded exercise therapy, was formerly the Chair of the British Association for CFS and ME (BACME) and Principal Medical Adviser for Action for ME. IM has been paid honoraria by The@WorkPartnership for lectures on the occupational health management approach to managing long-term conditions (including CFS/ME) in the workplace, is the Academic Dean of the Faculty of Occupational Medicine and commented on the NICE guidelines on the management of CFS/ME on behalf of the Faculty. MM received an honorarium for a lecture in 2020 for ViiV, received financial support to attend the EACS 2021 conference (virtual) and ViiV EACS 2019 conference, and was a centre co-lead for the PACE trial. IN reports research grants received from NIHR and MRC to conduct clinical trials on complex interventions, not specific to CFS/ME, has served on several Data Safety Committee as an independent member for trials on complex interventions, one of which related to CFS/ME, and is Co-Chair of Wellcome Trust/Indian Alliance DBT Team Science Grant and Clinical and Public Health Research Centers Grants Committee. DLP reports grants from the National Institutes of Health and Sidney R. Baer Jr. Foundation for work unrelated to this paper, has received honoraria for continuing medical education lectures at Harvard Medical School and the American Academy of Neurology, royalties from Springer Nature for a textbook on Functional Movement Disorder, is a member of the Board of Directors of the FNDS, senior (paid) editor of Brain and Behavior and is an Editorial Board Member of Epilepsy & Behavior. WP reports occasional paid lectures pertaining to FND (most payments donated to charity), has received fees for expert testimony in court on a range of neurological topics including FND, is a board member of FND Hope and FND Action, and is on the board of directors of the BNPA. MR reports a grant from Elsevier, royalties from Oxford University Press, honoraria from UCB Pharma, LivaNova, Eisai, and Angellini and sits on a data safety monitoring board for IqVia Medtech. WR reports grants from the German Research Foundation, royalties from books, and fees for German legal opinions. AS was a member of the 2007 NICE Guideline Development Group for CFS/ME [CG53]. TS reports being a member of the Board of Directors and Membership and Liaisons Committee of the FNDS and being a member of the Functional Movement Disorders Study Group (Movement Disorders Society). MS was a co-principal investigator for the PACE trial and has led a trial of CBT for CFS/ME. He is current President of the European Association of Psychosomatic Medicine Current (unpaid) and was the previous President of the Academy of Consultation Liaison Psychiatry (unpaid). BS is a Council Member of the Association of British Neurologists and Medical Expert Committee member of FND Hope UK. JS reports grants from Scottish Government and NIHR; royalties from UptoDate, the Donald Baxter Lecture Award, Montreal, titled “Multiple Sclerosis at the limits”, personal fees from expert witness work, Secretary FNDS, Medical Advisor FND Hope, Medical Advisor FND Action, running a self-help website for patients with FND. DW reports consulting fees for expert opinions on patients in a prolonged disorder of consciousness, fees for occasional medicolegal and personal injury cases, member of NIHR grant Programme Supervisory Committee of a trial of vocational rehabilitation after head injury, Deputy Secretary to British Society of Physical and Rehabilitation Medicine (unpaid) and is employed at a nursing home where he sees 2-3 patients with functional disorders. SW reports honoraria from two talks on psychological impacts of COVID to Swiss Re during the pandemic, but neither covered CFS nor Long Covid. He is on the Board of the ESRC and am also a member of the Judicial Appointments Commission for which he receives renumeration. None are relevant to this paper. SW is also on the Board of the South London and Maudsley Foundation NHS Trust for which he receives no renumeration. SW reports receiving grants to research CFS and has published over 150 papers on this subject, including being an author on several RCTs relevant to this submission, but none within the last 36 months. VW is Head of the Collaborative on Fatigue Following Infection (COFFI) (unpaid). AZ reports fees for expert witness medicolegal reports, but not in cases specifically focused on CFS/ME. No other authors declared any relevant competing interests.

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