Anomalies 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 aid recovery. This U-turn in recommendations from the previous 2007 guideline is controversial.

We suggest that the controversy stems from anomalies in both processing and interpretation of the evidence by the NICE committee. The committee: 1) Created a new definition of CFS/ME, which "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) Minimized the importance of fatigue as an outcome; 5) Did not use accepted practices to synthesise and GRADE trial evidence; 6) Interpreted GET as mandating fixed increments of change when 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 dissonance between this and the previous guideline was the result of deviating from usual scientific standards of the NICE process. The consequences of this are that patients may be denied helpful treatments and therefore risk persistent ill health and disability.

Introduction

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME), is a disabling long-term condition, characterised by severe fatigue, and other symptoms that are typically made worse by minimal physical or mental exertion (post-exertional fatigue and malaise).[1, 2] In addition to fatigue, other common symptoms include cognitive difficulties, sleep disturbance, and muscle pain.[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] The NICE 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 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 of the core illness itself.[6]

Such a substantial change to the previous recommendations would be understandable if the balance of the evidence had fundamentally changed. An internal NICE Review in 2017 had concluded that there was no new evidence to justify a revision of the previous guideline. Table 1 provides the conclusions of the meta-analyses of behavioural intervention trials published since 2007. Although some reviews mentioned limitations in the evidence, every review concluded that CBT and GET improved fatigue and other outcomes.

Table 1. Summary of meta-analyses published since 2007

Meta-analyses	N of trials*	Conclusions
Price, 2008[7]	15 (only CBT)	"CBT is effective in reducing the symptoms of fatigue at post-treatment compared with usual care, and may be more effective in reducing fatigue symptoms compared with other psychological therapies."
Malouff, 2008[8]	13	"Results indicate that CBT for chronic fatigue syndrome tends to be moderately efficacious."
Castell, 2011[9]	20	"The results suggested that both CBT and GET are promising treatments for CFS, although CBT may be a more effective treatment when patients have comorbid anxiety and depressive symptoms."
Marques, 2015[10]	16	"This meta-analysis of behavioral and psychological interventions targeting graded activity suggests that these interventions have sustained beneficial effects on chronic fatigue management, in particular on fatigue severity reduction for which a medium effect was found."
Smith, 2015[11]	21	"Trials of rintatolimod, 9counselling therapies, and graded exercise therapy suggest benefit for some patients meeting case definitions for CFS, whereas evidence for other treatments and harms is insufficient."
Smith, 2016[12]↑	16	"Rintatolimod improves exercise performance in some patients (low strength of evidence), while counselling therapies and GET have broader benefit but have not been adequately tested in more disabled populations (low to moderate strength of evidence)."
Larun, 2019[13]	8 (Only GET)	"Exercise therapy probably has a positive effect on fatigue in adults with CFS compared to usual care or passive therapies."

Casson, 2022[14]	14↓	"Activity pacing interventions are effective in reducing fatigue and psychological distress and improving physical function in CFS, particularly when people are encouraged to gradually increase activities."
Ingman, 2022[15]β	15	"Results suggest some support for the positive effects of CBT and GET at short-term to medium-term follow-up although this requires further investigation given the inconsistent findings of previous reviews."
Chou, 2022[16]	22	"Cognitive Behavioral Therapy (CBT) and exercise therapy were associated with improved fatigue, function, and other outcomes versus inactive control therapies, but the magnitude of effects based on average benefits was small to moderate. … The strength of evidence supporting the use of graded exercise and CBT was low and the magnitude of benefits was small to moderate, with inadequate evidence in patients diagnosed with more current case definitions, limited reporting of harms, and inadequate evaluation in severely affected patients."

* Number of trials of behavioural interventions reviewed

↑ Reanalysis of Smith 2016 excluded trials using Oxford definition of CFS

↓ "Activity pacing" interventions included CBT and GET

β Systematic review, not a meta-analysis

Yet despite the findings of these reviews, NICE decided to revise the 2007 guideline. This revision has met considerable opposition.[17] Three clinicians working in the field, who were on the NICE guideline committee, resigned before publication.[18] 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."[19] And: "CBT remains a valuable treatment for alleviating symptoms in CFS/ME and services should ensure patients have access to this… ."[19] 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."[20]

So, what went wrong? In this article we raise concerns regarding the evidence synthesis, appraisal and interpretation that appear to have underpinned the revised guidance.

The uncontroversial conclusions about CFS/ME in the guideline

First, 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] Some of the main points of agreement are summarized in box 1.

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 there are no diagnostic tests
- 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

The changes in recommendations regarding the management of CFS/ME

We suggest that the changes in recommendations concerning the management of CFS/ME derived from the processes chosen for identifying and synthesizing data for the NICE guideline. For full details of concerns over the review process, please refer to the responses to consultation of 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.[21, 22] There was a remarkable consistency in the criticisms made by these organisations.

Box 2. Eight anomalies of the NICE committee's CFS/ME 2021 guideline process and conclusions

- The use of a new definition of CFS/ME downgraded the certainty of trial evidence
- Omission of outcome data from standard trial end points used to assess efficacy
- Discounting trial data when assessing treatment harm in favour of lower quality reports
- Minimization of the importance of fatigue as an outcome
- Non-standard use of GRADE to assess the trial evidence
- Interpretation of graded exercise therapy as mandating fixed increments of change when trials defined it as collaborative, negotiated, and symptom dependent
- Inconsistency with NICE recommendations of rehabilitation for related conditions, such as chronic primary pain

- Recommendation of an energy management approach in the absence of supportive research evidence

1. Use of a new definition of CFS/ME 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 appearing to have been guided by the Guidelines International Network checklist for modifying disease definitions,[23] 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.[24] 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 as indirect evidence all those trials that had not specifically and explicitly required participants to report the symptom of PEM as a mandatory criterion for recruiting participants.[25, 26, 27] As this was a newly created definition, it down-graded nearly thirty years of research.

The emphasis NICE placed on PEM is debatable.[2, 28] Its prevalence varies according to how the symptom is defined and it is not specific to CFS/ME, being found in many conditions which present

with pathological fatigue.[29-32] PEM is also subjective, by definition, as are all the symptoms that make up the syndrome of CFS/ME. In contrast, the guideline authors criticised 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.[25] As NICE concluded: "The [established] diagnostic criteria have not been evaluated in terms of their measurement validity and accuracy in diagnosing ME/CFS."[25] 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 mandate PEM, although it is an optional symptom of the CDC definition.[24, 33] PEM is common in populations of patients with CFS/ME. Some 85% of participants reported PEM in eight CBT trials available for consideration, the prevalence depending on its definition.[34] An individual patient data analysis found no moderating effect of PEM on the impact of CBT on either fatigue or functional outcomes.[34] 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 and did not include the data from the eight trials mentioned above.[27]

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.[35] 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 therapy and usual care.[36] Indeed, PEM improved more with CBT and GET compared to the comparison treatments.[36]

In summary, adopting PEM as a mandatory symptom for previous trial participants was not based on robust evidence. Therefore, downgrading the certainty of evidence on this basis (of indirectness or applicability) was inappropriate.[26, 27]

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

The NICE committee did not use data from all time points and overlooked predefined end-point timings of trials. To comprehensively assess treatment effects over time, meta-analyses should use all time points that directly evaluate the treatment effect.[37] 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 only considered outcomes for each trial at the data point furthest away from randomisation.[26, 27] 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 is unconvincing.[38] The decision sometimes led to excluding consideration of earlier trial outcomes assigned *a priori* as primary end-point times.[26, 27]

Most trials only published outcomes at the predefined trial endpoint. The primary end-point for the PACE trial was at 12 months;[36] trial participants were also followed up naturalistically 2.5 years after randomisation;[39] some two years after the allocated treatment had ceased. By this time, 44 per cent of PACE trial participants had received either another course of the original therapy allocated or another trial therapy.[39] 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.[39] 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.[39] This naturalistic follow up finding was used by NICE to conclude incorrectly that these treatments were essentially ineffective.[26] The 6 and 12 months' findings of clear benefit for both CBT and GET, from the largest clinical trial in the literature, were not evaluated. [26, 27, 36] A cursory look at other current NICE guidelines to related or overlapping long-term conditions shows that this is not standard practice for NICE.[40]

3. Discounting trial data when assessing treatment harm in favour of lower quality reports

Harm is a critical issue to consider for all treatments, including 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. The NICE committee inverted the usual evidence hierarchy by not adequately considering the reassuring evidence of the low risk of treatment harms found within randomised controlled trials, of GET in particular. Instead they prioritised qualitative studies and patient organisation surveys.[26, 27]

Although the latest meta-analysis suggested that previous trials had limited reporting of harms,[16] some relevant data are available. Both the PACE trial and a more recent trial systematically examined six measures of harm in all participants and found no evidence of harm after GET relative to comparison interventions.[35, 36, 41] NICE were also provided with a summary of a meta-analysis of harm data from all ten published trials of GET.[42] This meta-analysis found no excess evidence of harm in relation to either the number of participants withdrawing from GET or rating their overall health as worse after treatment, when compared to controls.[42] 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 the intensity of the initial exercise.[42] So, whilst systematic studies of the safety of GET found no convincing evidence of harm with GET, NICE concluded that GET was not safe.

4. Minimization of the importance of fatigue as an outcome

The NICE committee decided to downgrade all fatigue outcomes based on the premise that it is a subjective measure.[26] 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. All these symptoms were 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.

The NICE committee took the view that therapy trials not being "blinded", with both participant and therapist being aware of the intervention, impaired the validity of the results.[26] Trials of complex non-pharmacological interventions often necessitate non-blinding of participants and therapists.[43] Interestingly, 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.[44]

The NICE guideline provided a description of what CBT entails.[6] It suggested 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 CBT was developed to do or how it was delivered in the trials for CFS/ME. The primary intention of CBT in the context of CFS/ME is to improve fatigue and function. We are not aware of any trial of CBT that had relief of distress as its primary outcome. Suggesting that CBT should only be used to manage symptoms and reduce distress associated with having a chronic illness implies that there is a "core illness" that CBT cannot change.[6] This assumption is puzzling given that CFS/ME is defined purely in term of symptoms and impaired functioning. If the symptoms resolve and there is a sustained return to normal life, then the patient has recovered. A treatment such as CBT that reduces fatigue and improves functioning is therefore a treatment that improves the condition, as the clinical trial evidence shows (Table 1).

5. Non-standard synthesis of GRADE to assess trial evidence

Based on the published reviews of the trial evidence, we consider that the research evidence was not presented adequately by NICE, resulting in the decision-making process being less robust. The application of the GRADE Evidence to Decision framework fell short of international expectations.[45] 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.[37] 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 aggregated groupings. This did not happen. The NICE evidence tables were so disaggregated it is hard to interpret them.[26, 27] The analysis was mainly at the level of the individual trial, which resulted in lower power and increased uncertainty in regard to primary outcomes.[26, 27]

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…".[19] The original GRADE (Grading of Recommendations, Assessment, Development and Evaluations) methodologists described the review as "…a disastrous misapplication of GRADE methodology,…"[45]

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

The description used by NICE is inconsistent with that of the 2007 guideline and trials of GET. In the current guideline, NICE described GET as incorporating fixed increments of exercise that are pursued irrespective of how the patient feels. We have been unable to find any trials that prescribed fixed increments of exercise. Trials and the previous guideline suggest that in GET, activity is determined

collaboratively with the patient and only increased as the patient feels able, dependent on their symptomatic response. Table 2 illustrates important examples of this from: the very first RCT, the previous NICE guideline, the largest trials of GET and the Cochrane review of exercise therapy. Supplementary table 3 provides examples from all the other trials of GET. So, there are no "fixed increments of exercise" in GET. The current guideline does describe an exercise programme, for those who wish to try it, but does not reflect the protocols used in the trials.[6, 13]

Table 2 Descriptions of GET prescriptions

Trial/review/guideline	Description of GET incremental approach
Fulcher, 1998[46]	"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." [our italics]*
NICE, 2007[4]	"When the low-intensity exercise *can be sustained [our italics]* 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…"
White, 2011[36]	"If it [exercise] can't be done every day, then the starting level is too high … 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."
Clark, 2017[35]	"Importantly, if a participant found that their symptoms increased after an incremental change in their activity, they were advised to maintain their activity at the same level for longer than a week, *until symptoms had settled, [our italics]* before considering another incremental increase."

Larun, 2019[13]	"Graded exercise therapy is characterised by establishment of a baseline of achievable exercise or physical activity, followed by a negotiated, incremental increase in the duration of time spent physically active followed by an increase in intensity."

7. Inconsistency with NICE recommendations of rehabilitation therapies for related conditions, such as chronic primary pain

NICE published a guideline for the management of chronic primary pain in 2021,[40] six months before the CFS/ME guideline. Chronic primary pain includes disorders such as fibromyalgia, which overlaps substantially with CFS/ME in terms of comorbidity and current aetiological and mechanistic thinking.[47] Population-based studies show a considerable overlap between these two conditions.[48] Indeed, the term 'myalgic' in 'myalgic encephalomyelitis' highlights how commonly people with CFS/ME experience pain.

Despite the strong clinical overlap, the conclusions were quite different in the primary pain guideline. For chronic primary pain, NICE recommends rehabilitation therapies, including graded exercise and psychological therapy.[40] 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 reduce fatigue and improve mobility.[49] This inconsistent approach is confusing for the outside world.

NICE responded to these criticisms by suggesting that the pain in CFS/ME differs from that found in conditions such as fibromyalgia.[21, 22] The new guideline refers the reader to the NICE guideline on neuropathic pain.[6] However, the pain of CFS/ME is not neuropathic pain, which is caused by a lesion or disease affecting the somatosensory nervous system.[50] 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.[50] The category of nociplastic pain, which is equivalent to chronic primary pain, is the correct category for the pain of CFS/ME.[51]

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

Having 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. NICE recommended this approach based on the experience of the guideline committee, yet the (limited) research evidence suggests otherwise. The only substantial evaluation of pacing for CFS/ME published to date was as one arm of the PACE trial.[36] This 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.[36, 41]

Conclusions

The new guideline includes important statements about the nature and consequences of CFS/ME. But, in regard to management, we have presented evidence that suggests that both the processes of synthesis of the evidence and decision making were problematic. It is difficult to understand the disconnect between the initial 2007 guideline that recommended CBT and GET, for which the research evidence has strengthened over the following decade, and the recent guideline that removes GET, qualifies CBT, and replaces them with "energy management", for which there is little evidence. We are concerned that this new guideline will effectively deny clinicians the ability to offer GET and evidence based CBT to those patients who want them and risks perpetuating chronic ill health and disability.

Since the guideline was published, three new systematic reviews have been published.[14-16] The forthcoming individual patient data meta-analysis of exercise therapy trials for CFS/ME is a further step in the right direction.[52] NICE should now reconvene a panel with an appropriate mix of specialists, methodologists, and patients (both recovered and those still unwell), to revise the guideline, based on these new reviews. In the meantime, both patients and clinicians may wish to remember that NICE guidelines are advisory, not mandatory. Finally, there is also a great need for more rigorous clinical trial research into novel interventions for those who do not respond to either CBT or GET.

Contributorship

PDW drafted the manuscript. All authors have contributed equally and have commented on iterative drafts and agreed the final version.

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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 (not specifically CFS/ME), 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 Functional Neurological Disorders Society. 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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