

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

Appendix 3: Expert testimonies

NICE guideline <number>

Appendix

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Draft for Consultation

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1 Jonathan Edwards

Section A: Developer to complete	
Name:	Professor Jonathan Edwards
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Institution/Organisation (where applicable):	University College London
Guideline title:	Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management
Guideline Committee:	6 th September 2019 at the Holiday Inn Regents Park
Subject of expert testimony:	The difficulties of conducting intervention trials for the treatment of myalgic encephalomyelitis/chronic fatigue syndrome.
Evidence gaps or uncertainties:	
Section B: Expert to complete	
Summary testimony:	<p>Therapeutic trials for ME/CFS are particularly at risk from expectation bias because of the subjective core features and fluctuating nature of the illness. Therapist-delivered treatments, with lack of blinding, and particularly those involving cognitive intervention, are even more at risk because of role-playing and deliberate influence on attitudes to health status. Trials of drug treatments have tended to navigate difficulties adequately but have yielded negative (or equivocal) results. Trials of therapist-delivered treatments to date have not met basic requirements for minimising bias and are therefore unsuitable as an evidence base for treatment recommendations. Inasmuch as they are interpretable, they suggest that although attitudes to health status may be influenced this does not lead to significant improvement in objectively measures of disability. There are also specific ethical concerns with trials of treatments that aim to persuade patients of an unproven theoretical model for their illness and for which there is prima facie evidence of significant harm (for exercise therapy). The failure to meet basic requirements indicates a problem with quality control through peer review in this area, as illustrated with problems with Cochrane reviews (see bibliography: Vink and Vink-Niese, 2018; Vink and Vink-Niese, 2019). Trials to date have failed to make use of methods that can significantly mitigate difficulties with bias from subjective outcomes, but it may be that for unblindable treatments new forms of trial methodology will be needed if useful assessment is to be achieved. In my view, the uninterpretability of evidence from trials that fail to overcome</p>

basic difficulties, combined with ethical concerns, means that it is inappropriate to recommend either cognitive behavioural therapy or exercise therapies for ME/CFS.

The difficulties of conducting intervention trials for the treatment of myalgic encephalomyelitis/chronic fatigue syndrome.

Introduction

I have been asked to act as an expert witness for the NICE ME/CFS guidelines committee in relation to difficulties of conducting intervention trials for treatment of ME/CFS. The following comments lay out my views on what I see as relevant issues. I have taken an interest in ME/CFS over the last five years, having been asked to advise on research quality by charities and funding bodies. My prior professional expertise was in translational rheumatology/immunology. I managed patients with illnesses involving fatigue, including ME/CFS, but had no special interest in the illness at the time. My research focused on mechanisms and treatment of autoimmune disease, including the introduction of rituximab for non-haematological diseases. I was involved in both basic laboratory science and clinical trials, from pilot studies through to large proof of concept trials. Since retirement I have acted as expert witness in major patent cases involving interpretation of clinical trials.

When asked to review research into ME/CFS my general impression was that, apart from some useful epidemiology studies and some well-designed mechanistic and clinical studies with negative results, research quality was disappointingly low. In terms of intervention trials there also appears to be a mismatch in standards of evidence applied to pharmacological and non-pharmacological treatments.

For clinical trials of pharmacological agents directed at the illness itself, rather than intercurrent symptoms, there is a consensus that in the absence of positive studies with either adequate blinding or objective endpoints we have no reliable evidence of efficacy. I assume that no recommendations are likely to be made regarding pharmacological treatments for ME/CFS per se. I will refer to drug studies only to illustrate the difficulties that beset trials for ME/CFS in general and the extent to which they can be, and have been, navigated.

The situation for therapist-delivered treatments is more difficult. Despite a similar absence of positive studies with either adequate blinding or objective endpoints there is a lack of consensus on use of these treatments. Both cognitive behavioural therapy (CBT) and graded exercise therapy (GET) were recommended previously and I agree that the justification for their inclusion needs reviewing. Trials of these treatments highlight the difficulties posed by clinical trial design for ME/CFS and this needs to be addressed.

Difficulties Facing Trials of Treatments for ME/CFS

The central difficulty for trial design in ME/CFS is the high risk of systematic expectation bias in a fluctuating condition with subjective core features. Crucially, that means that trials must either be effectively blinded or outcome measures must be underpinned by objective evidence. My reading of the literature is that although these problems have been successfully navigated in some pharmacological studies, attempts to do so for trials of therapist-delivered treatments have been inadequate and have failed.

A number of detailed methodological problems have been identified with trials of CBT and exercise therapies for ME/CFS (see Wilshire et al., 2018; Vink and Vin-Niese, 2018; Vink and Vink-Niese, 2019). I think all are relevant, but I will restrict my comments to general problems relating to bias that I think take precedence over the detailed issues and make more or less all the trials to date unsuitable as a basis for treatment recommendation.

All the studies that claim to show benefit from therapist-delivered treatments in ME/CFS are unblinded trials that make use of subjective outcome measures. (Some exercise studies show objective changes in indices of fitness but that does not necessarily imply a

reduction in illness or disability.) I would like to try to explain, in terms that those not trained in trial design can follow, why this is so critical.

The rationale for blinding in trials is that if either patients or researchers know which is the 'test' and which the 'dummy', when measures of results are subjective, then there is bound to be systematic bias towards a positive outcome for the test treatment. It is an aspect of human nature that affects all types of scientific experiment, whether in the lab or the clinic. If outcome measures are truly objective blinding is not necessary, and vice versa. For this reason, *unblinded trials with subjective outcomes* are specifically considered unreliable.

Reliability is never perfect, and it is reasonable to question how serious a problem this is. It has been considered critical enough for there to be a general policy not to accept the results of a drug trial using this methodology. But what justifies that policy and how relevant is to therapist-delivered treatments for ME/CFS?

A reasonable test of the unblinded/subjective outcome methodology is whether a trial of an inactive drug or a complementary therapy with no known active modality (e.g. cranial osteopathy) with that methodology would be likely to produce a spurious 'positive' result. Experience indicates that it would. In the past, unblinded studies have repeatedly shown positive results that disappear with blinding. This includes trials in ME/CFS with agents such as antivirals and rituximab, the latter providing a useful yardstick.

In an open label rituximab study from Norway major improvements in outcome measures were seen after rituximab usage for up to three years (see Appendix 1), but a subsequent blinded study showed that there was no real drug effect, again with a high (35%) response on placebo (Fluge et al. 2019). Because of 'positive-thinking' role-playing by all concerned, which will contribute to an apparent 'placebo effect', we can expect unblinded trials to give an apparent positive result whenever those providing the therapy encourage patients to think it will work. Although PACE authors and colleagues have claimed that placebo effects are likely to be small and of short duration in ME/CFS the rituximab studies indicate *this is not so*. In other words, unblinded trials like PACE provide us with no useful information, because a treatment with no specific beneficial action can give the same result. This is particularly true of large trials where systematic bias is more likely to show up as a 'significant' difference using standard statistics.

In addition, despite some claims to the contrary from authors of ME/CFS trials, ME/CFS is usually considered a high-risk condition in terms of subjective bias. That has to be the case if psychological factors are thought to be important in symptomatology; when I mentioned facilitating a drug trial for ME/CFS to the head of medicine at UCH his only comment was that for ME/CFS we would need to be 100% sure of blinding.

Then there is the question of whether therapist-delivered treatments such as CBT and GET are likely to suffer from relatively low or high risk of subjective bias in comparison to drugs. These treatments can be expected to carry the highest risk of all because deliberate induction of subjective bias is inherent in the theoretical model the treatments are based on. Patients are actively encouraged to take on a positive subjective state as part of their role in the treatment. Knoop, White and colleagues (2007) actually claimed that CBT operates through this mechanism, *as a placebo does*.

The SMILE trial provides useful confirmation of this problem, as it produced an apparent positive result for the Lightning Process, for which there is no reason to think any particular ingredient has a specific therapeutic effect over and above general role-playing.

Direct comparisons of similar therapy regimens, but with specific differences, might reveal components with efficacy, with less risk of bias, but neither PACE nor SMILE, nor the heterogeneous exercise trials included in the Cochrane review by Larun et al. (2017) help in this regard as far as I am aware. (CBT and GET, which overlap, gave much the same result in PACE, so the comparison does not help.) The default assumption is that the results of all these studies reflect a common role-playing bias (see also Wilshire et al. 2018). Moreover, because trials involve *trial-specific role-playing* there is no guarantee that even this will apply in routine practice.

The problem of not knowing what, if anything, is an active ingredient in these treatments is relevant to claims that poor results may reflect inadequate therapist training. [REDACTED] has expressed this concern to me, as a reservation about using PACE to justify rolling out treatments. The irony is that since we have no idea what, if any, aspect of treatment produces a useful effect we cannot know what 'adequate training' would be.

The presumption that it is possible to know how to delineate good practice in the absence of any controlled evidence is a salient feature of the literature right back to early papers. Wessely, Chalder and colleagues (1989) describe CBT for ME/CFS in a paper that includes at least a dozen instances of the word 'should' in advising on use of the therapy. Yet this is at a stage when no formal attempt to gain evidence of efficacy had been made. This raises major concerns about the validity of the whole treatment development programme.

It has repeatedly been claimed that the use of unblinded trials with subjective outcomes is justified by the difficulty in blinding therapist-delivered treatments. This is reflected in page 26 of 'Clinical Trials in Psychiatry' by Everitt and Wessely (2008) where blinding is described as 'desirable', rather than imperative, without adequate reference to the subjectivity problem. Blinding often accounts for a large proportion of the cost of a trial, because of the need for additional personnel. Drug companies would not spend many hundreds of millions of dollars a year on blinding if it were merely 'desirable'. In the context of subjective outcomes, it is *necessary* in order to get reliable results.

If results are unreliable, *they cannot be considered reliable just because it is difficult to get more reliable ones*. That this spurious issue is repeatedly raised just emphasises the existence of the difficulty. Moreover, methods for mitigating the difficulty exist. The American College of Rheumatology criteria of improvement for rheumatoid arthritis, rather than summing scores from disparate variables, uses a multiple threshold system so that a single improvement index indicates that key subjective outcomes are corroborated by relevant objective ones. I am not aware that tools such as this have been applied to ME/CFS trials.

In summary, the general principle that trials with subjective outcome measures must be blinded for test against dummy is even more relevant to therapist-delivered treatments than it is for drug treatments. Trials of this design cannot be taken as providing information reliable enough to base clinical practice on. Otherwise, any ineffective therapy could qualify for inclusion in guidelines.

There are a number of other difficulties relating to bias in trials of therapist-delivered treatments for ME/CFS but perhaps three should be mentioned.

Firstly, an additional difficulty with unblinded trials is that the analysis procedure has to be finalised *before the trial starts*, not just before data is analysed. In ME/CFS trials there has been a lot of what is, in effect, post-hoc analysis, with adjustment of primary outcome measures. The general problem with post-hoc analysis is again illustrated by the suggestion of a positive result in the blinded phase 2 study of rituximab in ME/CFS. A re-analysis at six months seemed to give a significant result. However, the phase 3 trial showed this to be spurious. Importantly, in the rituximab case the authors made it transparent that the phase 2 analysis was post hoc. This has not tended to be the case for trials of therapist-delivered treatments.

Secondly, for unblinded trials it is essential to avoid aggravating imbalance in expectations of efficacy in trial promotion. On several occasions perceptions of treatment benefits may have been unnecessarily coloured by advertising claiming that test treatments are effective. The adaptive pacing arm of PACE was argued to be a comparable 'active control' but it is clear that the role-playing expected with pacing was different from CBT and GET. CBT and GET were billed as effective treatments in terms of recovery and delivered by *therapists likely to have believed that*. 'Adaptive pacing' will have had a different psychological context. Billing of treatments as effective in advance of a trial has also occurred in studies on children. The problematic background psychology was highlighted by the comment by Richard Horton in a video at the time of PACE publication. He had apparently been told that PACE was about a 'clash of philosophies' between psychologists and patients – hardly an impartial scenario.

Thirdly, trials of therapist-delivered treatments are likely to suffer recruitment bias relating to perceptions of appropriateness of modalities in a way that will compound expectation

bias. Patients recruited to studies are likely to be relatively well disposed to the trial therapies. Patients may have seen a CBT trial as a way to get NHS CBT that otherwise they would have had to wait for – less likely for ‘adaptive pacing’ since pacing is normally self-managed. Patients who had experienced intolerance of exercise (characteristic of ME) would be likely to be put off trials involving GET. These difficulties are not easy to solve, but they need solving. As indicated below, methodology for trials of these treatments may need to be significantly different from the standard format.

In the context of these problems, the best we can probably expect from such studies is to glean a negative result, despite confounding effects of positive bias towards test treatments. Maybe we can. Follow-up results from PACE showed no advantage of CBT and GET over comparators. Objective measures retained in the final PACE analysis showed no convincing evidence of reduction in disability. The trial appears to refute the model that beliefs about health status perpetuate disability. At least in terms of subjective reports, beliefs appeared to change but *without any significant change in disability*, suggesting that beliefs are *not* the cause of disability.

A final point; the true gold standard for clinical trials is a combination of randomised, adequately controlled/blinded studies showing efficacy, *plus* corroboration from things like a dose response relation or a consistent time profile of response (kinetics). Dosing and kinetic studies are typically done first, and large controlled trials not set up until a minimum effective dose, dose response relation and kinetic profile have been documented, even if not with full statistical power. Without establishment of these initial data it is always difficult to be sure that a specific active modality has been identified and can be delivered in a reproducible fashion. For trials of therapist-delivered treatments there are few, if any, such data available.

In summary, trials in ME/CFS, in particular those using therapist-delivered treatments, suffer from several fundamental flaws. The PACE trial was intended to be definitive for CBT and GET but suffers from the same flaws. In their most recent response to criticism the PACE authors fail to address these issues (see Kindlon and Wilshire, 2019.)

Difficulties Associated with Theoretical Grounding

Strength of theoretical grounding is not usually a key factor in clinical trial quality but poses difficulties for CBT and GET trials because theory intrudes into treatment delivery. Both appear to be delivered in a framework of assuming that patients have unhelpful beliefs about their activity capacity that can be overcome by a therapist. As far as I can see there is no evidence to indicate this assumption is more than popular prejudice. The only argument I have seen used is that strong belief in being organically ill is associated with lower chance of recovery. However, the alternative hypothesis – that the patients’ beliefs are accurate - predicts the same finding. The only further evidence I am aware of comes from the results of trials. PACE, if anything, refutes the hypothesis because apparent changes in beliefs were *not* associated with objective evidence of lesser disability.

There is also a built-in problem with the theoretical model in terms of drawing useful conclusions from trial results. The unhelpful belief model on which CBT is based assumes the patient’s self-reported assessment of their health status *does not* reliably reflect functional potential, which is what patients want to improve (even if it reflects current limitations). It is no good then to take *final self-assessments* as a reliable index of functional potential. There has to be consistency in the interpretation for it to be valid.

In manuals for health professionals there appears to be a continuing confusion between objective and means. All can agree that the objective is increased activity, but that does not imply that the means should be to increase activity. In athletic training an objective is to reduce resting heart rate, but the means is to increase heart rate. The original GET theory was based on an analogy with the discomfort induced by athletic training. This analogy does not apply in a simple manner since the response in people with ME/CFS is different. The theory has to accept this difference may be the basis for a different, *adverse*, long-term response in terms of stimulus tolerability. The theoretical base does not appear to have been validated with physiological measures in the way one might expect before application to treatment.

Cardiopulmonary testing provides at least suggestive evidence that the physiological response to activity is different in ME/CFS (Keller et al., 2014).

The broader question arises as to whether there is any consistent background model that is still viable in the light of evidence. My understanding is that evidence for deconditioning in ME/CFS is unconvincing and certainly does not explain symptoms. Improvement with the Lightning Process, for which trial evidence is probably on a par with GET, and also with the Norwegian Mindfulness programme, has been described within a few days of intensive engagement, again suggesting that deconditioning is not the limiting factor. Evidence of efficacy is paramount but since both CBT and GET involve 'educating' patients in a theoretical background the shakiness of this background is an additional concern.

The above concerns are expressed despite claims from those doing research into CBT and GET for ME/CFS that this is high quality science, distinct from alternative medicine. I would like to think that was the case. However, in reality there seems to be no dividing line between studies of CBT and GET and studies of alternative therapies such as the Lightning Process, and the Mindfulness approach developed in Norway. All appear to be based on unsubstantiated theory and none validated by adequately designed trials.

Ethical Difficulties:

The above considerations imply that, in addition to efficacy and safety concerns, there are specific ethical difficulties both with trials and service provision of CBT and GET.

Patients are entitled to be fully informed, based on reliable evidence. As I understand it, patients receiving CBT are not told that the explanation given for the illness is speculative, that there is no reliable evidence for the efficacy of the treatment or that objective measurements and long-term follow-up suggests there is none of consequence. Convincing the patient that the explanation of the illness is correct, and that the treatment is effective, appear to be inherent to the way CBT is supposed to work. It would therefore appear to be unethical to continue development and use of CBT based on the current approach of altering beliefs about e.g. disease causation or effects of exercise.

GET is justified on the basis that inducing a positive change in perceptions of ability to tolerate exertion indicates a genuine physiological improvement. However, a large number of patients have reported a seriously negative change in perceived ability to tolerate exertion after GET in routine practice (see Kindlon, 2017). To be consistent, this must equally be considered a genuine deterioration in physiological status. Moreover, it is plausibly attributable to GET, since the perception relates directly to the experience of GET. It is not justified to regard improvement in reported status as a valid index but deterioration as not. ('Biopsychosocial' theorists are not in a position to deny harm on the grounds that worsening is 'just psychological'.) Although the use of GET is based on a hypothetical desensitisation of patients to adverse symptoms following exertion it would be equally plausible to expect hypersensitisation, so there is no theoretical reason for ignoring reports of deterioration. On a biopsychosocial model that gives attitudes a key role in determining health status, significant negative change seems, if anything, to be a particularly plausible outcome.

As I understand things, the prima facie evidence is that, on the criteria used as outcome indicators in these studies, significant numbers of patients may be harmed by GET. In this context, I think it would be unethical to continue the development and use of GET.

Quality Control

As indicated above, difficulties encountered with clinical trials for ME/CFS revolve around psychology – the psychology of our natural tendency as investigators to allow expectation bias to creep in and how to guard against that. Avoiding bias requires quality control through peer review by people who understand and acknowledge the difficulties. Clinical pharmacologists have taken note of the psychology of drug trials. Those involved with therapist-delivered treatments need to do the same.

Reviewing clinical trials in CFS/ME came as something of a shock to me in terms of methodologies considered acceptable. I advised the UCLH physiotherapy department on research project design in the 1990s. It was clear then that unblinded studies with subjective outcomes were not capable of producing usable efficacy results. That fuelled a move to 'qualitative studies' that documented natural history without providing efficacy evidence. It was recognised that therapist-delivered treatments often had no adequate evidence base.

What surprised me about PACE and other trials in ME/CFS was not so much that therapists were still using unproven treatments but that anyone should think it worth doing expensive formal trials with inadequate methodology. Liaison psychiatry and neuro-rehabilitation appear to have got into an unfortunate situation in which therapist-delivered treatments are introduced into routine care following flawed assessment of efficacy and safety. This suggests that the peer review system has broken down.

Peer review problems were highlighted to me with a manuscript of my own. It was recommended that I not mention problems with unblinded trials, not because my critique was wrong but because it would cast doubt on almost all treatment studies in clinical psychology. One referee asked specifically for removal of such comments. Something is badly wrong; the disciplines involved need to take a long hard look at their standards of evidence. The broader context of this is well described in Hughes's '*Psychology in Crisis*' (2018).

A number of psychiatrists and psychologists involved in these studies, including [REDACTED] and some PACE authors have claimed in public that they do not understand why there are problems with unblinded trials with subjective outcomes. As indicated above, there is nothing difficult to understand; all medical students should know about this (see <https://www.students4bestevidence.net/blinding-comprehensive-guide-students/>). In general medicine there is no disagreement on this. In a recent informal poll of 80 assembled members of the UCLH Department of Medicine at Grand Rounds all but one (who abstained) agreed that such trials are unreliable and unsatisfactory.

Recent comments by three PACE authors in a published response to critique indicate how little the difficulties of expectation bias are understood. The authors say that they prefer the altered outcome criteria that they introduced post-hoc because they gave results more consistent with previous studies and their clinical experience. They do not seem to realise that outcome measures need to be predefined in order to avoid *exactly this sort of interference* from expectation bias (see Kindlon and Wilshire, 2019).

A major reason for poor quality control in terms of conducting trials may be the anomaly that therapist-delivered treatments have not been subject to the licensing requirements for drug treatments. The lack of regulation for therapist-delivered treatments may reflect a perception that these treatments do not cause harm. However, there are good reasons to think that both psychotherapy and exercise therapy can do harm, particularly if they involve misrepresentation of knowledge about an illness.

Although therapist-delivered treatments pose extra challenges for trial design, trials to date have not made the best of the options available. Objective requirements can be worked into primary outcome measures (as mentioned above) without great difficulty while retaining key subjective elements. It may be, however, that significantly different methodologies need to be developed to get systematic information on the value of therapist-delivered treatments because of the major confounding effect of theory-driven role-playing involved. As Geraghty (2017) points out, trials of therapist-delivered treatments may need to use delivery by people with no commitment to the treatments' likely efficacy. Trialists cannot claim that it is necessary for expert practitioners to be used since we do not yet know what works – i.e. who is 'expert'. Sham control procedures need to be designed so that any influence of theory-driven role-playing is neutral across comparisons. If role-playing is considered to be part of the therapeutic process it may be that the standard prospective controlled trial format cannot achieve what is needed. If so, considerable thought needs to go into alternatives, since current alternatives like service audits or 'pragmatic trials' are even more subject to systematic bias than formal trials.

Cochrane reviews have earned an important role in the peer review process, with the caveat that Cochrane has recently been criticised for over-favourable reports of treatments due

to lack of impartiality. In this context there is every reason to question the evidence for treatments where Cochrane expresses doubts.

The most recent Cochrane review of CBT for ME/CFS (Price et al., 2008) comes to a guarded conclusion about short term benefit and emphasises the need for more studies. Moreover, problems with the review being overoptimistic have been discussed by Vink and Vink-Niese (2019).

The most recent review of exercise therapy (Larun et al., 2017) suggested that there was some benefit, but the Cochrane editorial office has expressed serious reservations about the quality of the review and asked for the authors to withdraw it. An update has been abandoned. The situation with this review remains unresolved, with the most recent statement from Cochrane being: 'The author team will amend the review to address changes aimed at improving quality of reporting of the review and ensuring that the conclusions are fully defensible and valid to inform health care decision making.' There is a clear implication that Cochrane is not satisfied that the review is valid for healthcare decision-making.

In addition, there has been internal recognition that peer review has not functioned well in the Cochrane mental health section that generated these reviews and that opinions need to be sought more widely (expressly indicated to referees for the most recent review). Both the above reviews were authored by a junior departmental colleague of a PACE author. It is also of note that a founder member of Cochrane, Hilda Bastian, has recently expressed her view in a PLOS blog that patients' concerns about CBT and GET will prove valid.

As a disinterested outsider I think there is good reason to be concerned about quality control in this area. I do not have resources to search widely in the literature, but I suspect the problems of therapist-delivered treatments in ME/CFS extend into other areas and particularly the questionable category of 'Medically Unexplained Symptoms' (MUS). There appears to be a problem of mutual blinkering amongst those with an interest in such treatments with regard to evidence evaluation. (The content of a recent East London MUS Service video https://www.youtube.com/watch?time_continue=3&v=IEhyR9gRYJE suggests that adequate evidence evaluation remains a serious problem. The presentation even includes 'body psychotherapy' for which there seems to be no evidence base. The recent BACME National Services Evaluation Document also notes the problem of inadequate evaluation methods.)

In view of the above, in particular the discouragement of a critical approach by peer reviewers, I think it imperative that decisions on therapist-delivered treatments exclude those *whose jobs depend on provision of, or are involved in development or dissemination of, these treatments*, whether in the context of ME/CFS or the wider umbrella term MUS, used to include ME/CFS. Judging by traffic in the media I suspect that, apart from a major conflict of interest relating to personal career, both therapists and academics will be under strong peer pressure from colleagues to protect interests. Exclusion would be standard for drug evaluation; a level playing field is needed, especially in the context of increasing financial interest in terms of training and service provision (as indicated by Rona Moss-Morris's recent comments on commercial exploitation of service expansion). One would hope it would not be necessary to make such remarks but unfortunately the historical context in this field suggests otherwise, with recurring examples of concerns about inadequate declaration of conflicts of interest, not just from study authors but also from colleagues with interests by association. It is crucial that NICE ensures that those involved at all levels are truly impartial.

Implications for Recommendations

ME/CFS clinical practice guidelines need to reflect reliable evidence of efficacy and safety, as in other areas. It is my own view that CBT and GET should be removed from recommendation. Because of a failure to navigate adequately the difficulties associated with trials, recommendation is not supported by reliable evidence and there are significant ethical problems with their continued use. This applies both to adult and paediatric care.

As far as I am aware all patient support organisations are in favour of removing CBT (ME/CFS type) and GET from the guidelines or have serious misgivings, including Action for

ME, which was involved in PACE. My interactions with patient representatives indicate that these views are well founded and should be respected.

There is, however, a need for a service for patients to provide long-term support and diagnostic review. Until we have reliable information on specific modalities it seems that will need to be pragmatic, relying on empathy, realistic prognostic information and careful clinical assessment at regular intervals. My impression is that much more emphasis is needed on ongoing support, rather than the use of short treatment courses. Perhaps the greatest missed opportunity of trials focussing on stereotyped treatment modalities is a failure to recognise the value of support from experienced carers that simply aims to make life easier to cope with, rather than address a theoretical model.

Professionals such as occupational therapists and community nurses currently involved in ME/CFS services are likely to be well placed to continue to provide supportive care. Advice on levels of activity will inevitably feature in any such support. However, at present there appear to be no good grounds to make specific recommendations, other than to avoid aggravating symptoms. How to describe and categorise such support in a guideline may prove difficult but I think there are overriding arguments for ensuring that it is *not under the terminology of Cognitive Behavioural or Exercise Therapies* for the reasons given above. (CBT used in ME/CFS trials is not routine CBT and specifically suffers from the difficulties mentioned. Standard CBT for co-existent problems might be justified. However, I see no reason to include it in an ME/CFS guideline - it is bound to lead to conflation and confusion.) I have no doubt that professionals are committed to doing the best possible for patients but if ME/CFS management strategy is going to progress there is a need for a clean break from methods that lack sound supporting evidence and raise concerns about harm. Management needs to be dissociated from unproven models and the ethical problems they bring with them.

In broader terms, the NICE committee is likely to be under pressure to recommend a variety of treatments, from various viewpoints. At a scoping meeting it was suggested that there was a general view that 'different people respond to different treatments'. However, this is misleading, because in ME/CFS we have no adequate trials showing efficacy. We do not know if there are any 'responses'. This contrasts with, e.g., rheumatoid arthritis, where we do have evidence that different people respond to different treatments *from well-designed trials*. There is no justification for a range of unproven options. The only legitimate position I see is to make no recommendations for specific therapies and focus on supportive care. As Fiona Godlee said recently in the context of guideline recommendation: 'If we don't know, let's be silent'.

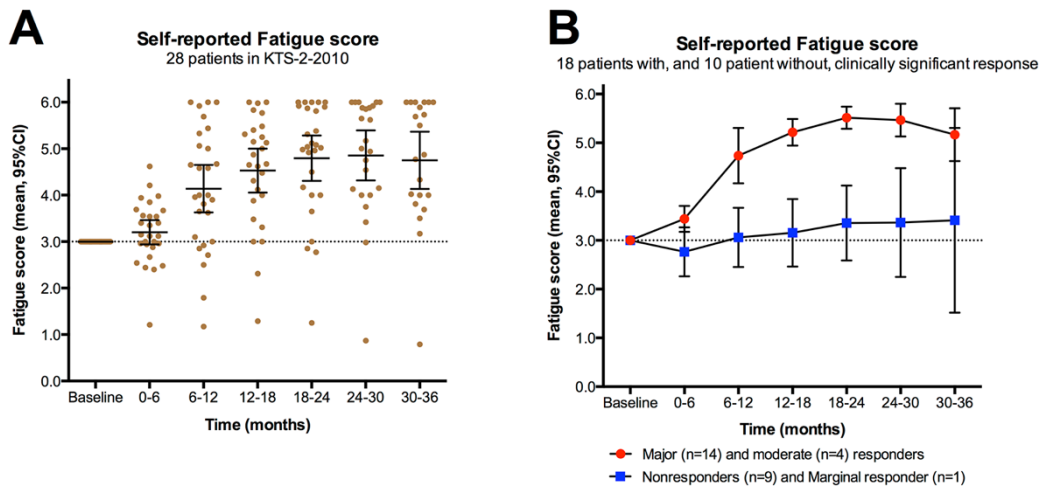
Declaration of Interests

I genuinely believe that I have no competing or conflicting interests (in the sense of potential benefits that might accrue to me or my close associates) beyond identifying evidence that can inform optimum recommendations for care of people with ME/CFS. I have no personal or professional interest. I do not have ME/CFS, nor do my family or close friends. I am retired from clinical practice. I have neither financial interests, nor any involvement in research grant funding other than as an advisor to research councils, charities and steering committees.

I have no commitment to a particular view of ME/CFS pathogenesis or treatment. It may be that long-term disability in ME/CFS is primarily due to a problem with brain signalling without structural change, classifiable as neurological or neuropsychiatric. In some cases there may be underlying metabolic or immunological changes. However, as yet we have no understanding of the illness, so I see categorisation as arbitrary and unhelpful.

I have had considerable contact with patients through internet groups over five years. I have done so in order to try to understand the illness as perceived by patients, interacting on an equal basis to avoid the role-playing that goes with professional-to-patient relationships. I agreed to act as a board director for one forum for a time, but now have no personal commitment to any patient-based organisation. I try to avoid statements that may cause unnecessary distress, but I am equally critical of any material under discussion, regardless of the slant of the theoretical model, as and where appropriate.

Appendix 1: Prolonged apparent benefit in and open label study of rituximab in ME/CFS. A subsequent blinded study showed no real effect.



References to other work or publications to support your testimony' (if applicable):

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2 ¹ **Nina Muirhead**

2

Section A: Developer to complete	
Name:	Dr Nina Muirhead BA(oxon) BMBCh(oxon) MRCS DOHNS MEd PGDipDerm
Role:	Expert on Medical Education in ME/CFS
Institution/Organisation (where applicable):	Buckinghamshire Healthcare NHS Trust
Guideline title:	Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management
Guideline Committee:	22 nd October 2019 at the Holiday Inn Regents Park
Subject of expert testimony:	Information, education and support for health and social care professionals providing care for people with ME/CFS.
Evidence gaps or uncertainties:	<p>The Department of Health in England has asked NICE to develop a guideline on the Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management.</p> <p>The committee are aware there is a lack of research evidence on what the information, support and education needs are of health and social care professionals providing care for people with ME/CFS and this was felt to be a gap in the evidence that should be addressed.</p> <p>Where the research evidence is lacking, or inconclusive, guideline committee members can invite expert witnesses to the group to provide their knowledge and experience, and recommendations can be drawn from this expert witness and Guideline Committee consensus.</p>
Section B: Expert to complete	
Summary testimony	

Thank you for this opportunity to use my experience of being a patient, healthcare practitioner and medical educator to provide a testimony on 'Information, education and support for health and social care professionals providing care for people with ME/CFS'.

I became ill with ME/CFS in 2016. I was severely affected for much of 2017 and am now moderately affected. My understanding and belief in the illness has completely changed since becoming ill. I have first-hand experience of the negative impact of ignorance of the illness among health and social care professionals and the harm it can cause. I have also taken the time to research undergraduate and postgraduate education and resources. This includes forging links and connecting with individuals in healthcare education roles in the UK, Scotland, Ireland and Wales as well as meeting with international colleagues involved with ME/CFS research and education.

In the UK our ME/CFS charities' websites are a fantastic resource for information, education and support, (1) but are not often accessed by health and social care professionals.

As a doctor I did not recognise the illness myself. Current education and information convinced me I did not have ME/CFS. I saw 13 different doctors before I was diagnosed. The information, education and support provided by the NHS (2), Healthcare Education England HEE (3), Universities (4) and Royal College of General Practitioners (5) is outdated, misleading and does not fit with the patient experience. Education based on theories of deconditioning and fear avoidance of exercise lead the professional to believe that the patient will respond to reconditioning and may recover with cognitive behavioural therapy (5). This is in direct conflict with the neuroimmune exhaustion, exacerbation of symptoms and post exertional malaise described by patients, supported by research showing that exercise deteriorates physical performance and increases lactate in patients with ME/CFS (6). The incongruity between current education of professionals and the experience of patients compromises the relationship between patients and health and social care professionals. Or worse has the potential to cause harm (7,8).

"In the past, ME/CFS has been characterized as a syndrome of medically unexplained fatigue responsive to talk therapy and graded exercise. But scientific advances are revealing a complex, multisystem disease involving neurological, immunological, autonomic, and energy metabolism impairments. There is a critical need for a different approach to management of the disease and accompanying comorbidities." (9)

Current UK ME/CFS education and training is not mandatory, often it becomes merged with other medically unexplained symptoms (MUS). Chronic Fatigue Syndrome is listed in the applied knowledge assessments for GPs but the type of knowledge expected is not expanded upon and the exam board have been reluctant to divulge past paper questions and marking schemes. Approximately one third of medical schools report teaching ME/CFS but the majority spend two hours or less on the topic. Only one in ten medical schools has reported that a student will meet a patient with ME/CFS as part of their training. None of the medical schools invited to share teaching resources on the topic were forthcoming. Information from the Scottish freedom of information study shows that this is taught as a medically unexplained illness (4). Those who are motivated to engage in postgraduate CPD modules on the topic such as RCGP CPD and HEE Unit 3.3 will learn the theory that patients are perpetuating their own illness, symptoms are caused by lying in bed and fear avoidance of exercise.

New education on this topic is required to reflect:

- 1) The huge paradigm shift in understanding of this illness
- 2) Up-to-date international biomedical research and education on ME/CFS
- 3) The experience of patients whose lives are completely changed by the illness

Summary:

Areas of Education:

Medical School Education, Health Education England, Royal Colleges, CPD, NHS Online Advice, Patient Information Leaflets

Target Audience:

Medical Students, Qualified Doctors, Health Professionals of all Allied Sectors (Physiotherapy, Dieticians, Nurses, School Nurses, Occupational Therapists, Complimentary Medicine), Occupational health and Social Care and Support.

Education is Currently:

Lacking, Based on Outdated Models of the Illness, Misleading, Harmful.

Lack of education and outdated theories are causing: Failed and delayed diagnosis, disrespect or disbelief, lack of engagement, lack of recognition, multiple referrals to different specialties.

Useful Education Resources:

ME/CFS Charities Websites, International Teaching Materials, ME Association 'Purple Book' and Index of Published Research, CDC, IOM, NIH, BMJ Best Practice.

Unpublished research has shown that medical students are interested in learning about this illness and medical schools are willing to receive information and support.

References to other work or publications to support your testimony' (if applicable):

- 1) <https://www.meassociation.org.uk/wp-content/uploads/ME-Association-Index-of-MECFS-Published-Research.pdf>
- 2) https://www.researchgate.net/publication/256293990_Graded_Exercise_Therapy_A_self-help_guide_for_those_with_chronic_fatigue_syndromemyalgic_encephalomyelitis
- 3) <https://www.hee.nhs.uk/sites/default/files/documents/CBT%20LTC%20MUS%20curriculum.pdf>
- 4) <http://www.forward-me.org.uk/Reports/Summary%20of%202017%20FOI%20responses%20from%20Scottish%20Medical%20Schools.pdf>
- 5) <https://elearning.rcgp.org.uk/course/view.php?id=93> RCGP e-learning CPD
- 6) Lien K, Johansen B, Veierød MB, et al. Abnormal blood lactate accumulation during repeated exercise testing in myalgic encephalomyelitis/chronic fatigue syndrome. June 2019. *Physiol Rep.* ;7(11):e14138. doi:10.14814/phy2.14138
- 7) <http://voicesfromtheshadowsfilm.co.uk/dialogues-project/>
- 8) Keith J. Geraghty & Charlotte Blease (2018) Myalgic encephalomyelitis/chronic fatigue syndrome and the biopsychosocial model: a review of patient harm and distress in the medical encounter, *Disability and Rehabilitation*, DOI: 10.1080/09638288.2018.1481149
- 9) <https://www.omf.ngo/2019/09/01/new-guidelines-for-diagnosing-and-treating-me-cfs/>

3 ¹ Mujtaba Husain

Section A: Developer to complete	
Name:	Dr Mujtaba Husain
Role:	Consultant Liaison Psychiatrist Associate Medical Director – Specialist Services
Institution/Organisation (where applicable):	South London and Maudsley NHS Foundation Trust
Guideline title:	Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management
Guideline Committee:	24 th July 2020
Subject of expert testimony:	The different models of multidisciplinary care, including team composition, for people with ME/CFS.
Evidence gaps or uncertainties:	<p>The Department of Health in England has asked NICE to develop a guideline on the Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management.</p> <p>There is a variation in the way services are delivered to people with ME/CFS, with care being led by different medical and professional specialities. There is a lack of research evidence on different models of care and approaches and this was considered to be a gap in the evidence that should be addressed.</p> <p>Where the research evidence is lacking, or inconclusive, the guideline committee can invite expert witnesses to the group to provide their knowledge and experience, and recommendations can be drawn from this expert witness and the committee consensus.</p>

Section B: Expert to complete

Summary testimony

I am a consultant at the Persistent Physical Symptoms Research and Treatment Unit, formerly the Chronic Fatigue Research and Treatment Unit. We are a multidisciplinary team with cognitive behaviour therapists, clinical psychologists, physiotherapy and consultant psychiatrists. Our service provides medical / biopsychosocial assessments with appropriate physical examination, laboratory investigations, formulation and diagnosis. We take a collaborative, patient centred approach in which patient choice is essential. We have broad eligibility criteria to ensure we do not exclude people from getting help. In terms of treatments we offer Cognitive Behaviour Therapy or Graded Exercise Therapy. We can also provide home-based treatment for the severely affected. Treatment takes a pragmatic approach to identifying and improving modifiable risk factors. Medical input from the psychiatrists within the multidisciplinary team is important to ensure other causes of fatigue are considered and to assess for mood disorders which are common in long term conditions. We also liaise closely with other specialists involved in our patients' care and take a mind-body approach to integrating physical and mental healthcare as is best practice for all long terms conditions.

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