10 year surveillance (2017) – Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy) (2007) NICE guideline CG53

Stakeholder consultation comments form - proposal for 'no update'

Consultation on the proposal for 'no update' opens on:
9am Monday, 10 July 2017

Comments on proposal to be submitted:
no later than 9am Monday, 24 July 2017

Organisation name – Stakeholder or respondent: #MEAction

Disclosure
Please disclose whether the organisation has any past or current, direct or indirect links to, or receives funding from, the tobacco industry.

We have no links to the tobacco industry. In terms of potential conflicts of interest, NS is an employee of Pfizer Inc and may own stocks in the company. The contents of this response are in no way endorsed by Pfizer Inc. None of the other authors declare any conflicts of interest.

Name of commentator: Jenny Lyus, Natalie Silmon de Monerri, Emma Shorter, Anna Wood (with contributions from George Berger, Leah Williams, Tanya Marlow, Sarah Reed and other #MEAction volunteers)

Please insert each new comment in a new row
Please email this form to: surveillance@nice.org.uk
If you wish to draw our attention to published studies, please supply the full reference.

Closing date: 9am, 24 July 2017

NB we had difficulty formatting the form. The Surveillance Team gave permission for us to create our own form layout.

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Question 1 Do you agree with the proposal not to update the guideline?	**No**

The Myalgic Encephalomyelitis Action Network (#MEAction) is an international grassroots network dedicated to working for health equality for patients with ME. #MEAction Network UK is the local affiliate operating in the United Kingdom. We are a patient voice in this consultation.

Our members are distressed about the proposal to not update the guidelines, as UK patients view an update to be an urgent necessity. Widespread patient concern is evidenced by the ME Association patient petition: "the current guidelines are not fit for purpose and require complete revision"[1] (14,757 signatures in less than two weeks).

In summary, the main NICE recommendations of cognitive behavioural therapy (CBT) and graded exercise therapy (GET) as treatments only make sense in the context of the causal CBT Model of CFS and ME (a psychosocial model), but we consider this hypothesis to have been refuted, so therefore the guidelines require updating for patients with ME (see 1h). The quality of evidence is lacking for us to feel safe in regards to the risk versus benefit of these treatments given the absence of theoretical justification (see 1b, 1c, 1d, 1e, 1g). In particular, graded exercise therapy is not considered by patients to be effective, acceptable or tolerable (1c, 1d, 1g). The body of research that these treatments are based on fails to meet our patient threshold of satisfactory scientific rigour which includes:

- Post Exertional Malaise (PEM) as a symptom in a recognised case definition (ME criteria such as the Canadian Consensus Criteria (CCC), or the International Consensus Criteria (ICC) and provisionally the CFS Fukuda Criteria, see 1a and 1i)
- Blinded trial and or objective outcomes (but never neither of these, see 1b)
- Satisfactory recording of harm (1d).

Instead we put forward some suggestions of patient-preference revisions for the new guidelines (see 1i, 1f, 1g). Evidence for our position on this is outlined below.

[1]ME Association 2017, Petition: The NICE Guidelines for ME/CFS is UNfit for purpose and needs a complete revision viewed 17th July https://www.change.org/p/petition-the-nice-guideline-for-cfs-me-is-unfit-for-purpose-and-needs-a-complete-revision

1a PEM and appropriate definition is key to effective treatment

Post Exertional Malaise (PEM), sometimes called Post Exertional Neuroimmune Exhaustion (PENE), is the key differentiating characteristic of ME (Institute of Medicine report, 2015; Jason et al., 2013; Maes, Twisk & Johnson, 2012). By definition, PEM is the loss of stamina/function and the post-exertion exacerbation of symptoms following even trivial amounts of mental or physical exertion, often with delayed onset.

In studies that only require chronic fatigue in the case definition, and therefore not the ME and CFS specific symptom of PEM, it is likely that participants with other fatiguing conditions are included. This confuses the results leading to inflated outcomes. This requires serious reconsideration as there cannot be relevant actionable findings from trials which do not properly define the patient population. When NICE includes studies which solely rely on the symptom of chronic fatigue, as in the Oxford criteria, the resulting recommendations are likely to include advice which is unsuitable (and possibly unsafe) for ME patients.

A study published this week shows that "85% of Oxford-defined cases were inappropriately classified as CFS". "The Oxford criteria designated CFS in 25.5% of 2004 males and 19.9% of 1954 females…[in contrast] Fukuda criteria identified CFS in 2.3% of males and 1.8% of females." (Baraniuk, 2017). This calls into question the relevance of any studies using the Oxford criteria which have been used as evidence for the current NICE guidelines (such as Fulcher 1997, Powell 2001 and 2004; Wearden 1998) as well as the large PACE trial.

The US Centers for Disease Control and Prevention have recently set a precedent by downgrading studies which use the broad Oxford case definition criteria - in which PEM is not included. The result of this is that their treatment website page no longer mentions CBT or GET as suitable for ME (see https://www.cdc.gov/me-cfs/). In addition, the U.S. Agency for Healthcare Research and Quality found evidence for CBT and GET was negligible after removing Oxford criteria studies from its analyses (Smith *et al* 2015).

Also, exacerbation of symptoms after exertion cannot be optional in ME, as is implied by the current guidelines (section 1.6.2.16). We feel that PEM does not feature prominently enough in the current guidelines (section 1.2.1.2).

1b The evidence for the efficacy of GET & CBT is unsound

(Re: NICE guidelines Section 1.6.3 more specifically CBT 1.6.2.8 GET 1.6.2.11 and Review Question-05 of your Proposal)

We would like to make clear that our concerns about methodology extend beyond the PACE trial to include the entire body of GET/CBT research, where it relies on the flawed combination of unblinded randomisation and subjective outcomes (Helmfrid, 2016). We ask that such clinical trials be excluded or downgraded.

The apparent effects of CBT or GET in these studies can be explained solely by study design: an unblinded trial using self-reported measures. This is supported by the recent (Stouten 2017) paper which showed that "the more objective the outcome, the worse the result for CBT and GET".

This flaw particularly applies to studies using CBT as a treatment for ME due to the nature of this specialised form of treatment. While we have no objection to the use of talking therapies as a tool to process the adversity of living with chronic illness, the CBT that has been advocated for ME aims to challenge thought patterns about the disease itself (see 1h). Evidence is lacking that this type of CBT produces any improvement in patients' physical capabilities in objective measures, such as return to work (McPhee G 2017). We assert that this combination of unblinded and subjective measurement creates a dynamic of participants being trained to answer the questionnaires 'better' rather than ensuring that the patients actually get better. As (Stouten 2017) has stated, "Though patients *think* they are able to walk more after CBT, they fail to actually do so".

1c Ineffective treatment cannot be cost-effective

For a treatment to be cost effective, it must demonstrate efficacy.

We consider the difference between the findings in the original PACE papers and the reanalyses to be substantially different. They cannot accurately be described as similar (as described on p3 of Surveillance Proposal Review). Alterations to the clinical protocol were made, which artificially presented GET and CBT as more beneficial than under the original protocol (Goldin, 2016). In contrast to the original analysis, which claimed that the majority of patients improve, after the PACE authors' own reanalysis a majority of approximately 80% did not improve. This could more accurately be described as opposite rather than 'similar'. Furthermore, the two year follow-up study also failed to show significant between group differences (Sharpe et al., 2015 cited in Geraghty forthcoming).

These unconvincing results are not confined to the methodologically flawed PACE trial; there is a pattern of long term, null between-groups results in other trials. The FINE trial, a nurse-led CBT based treatment for the more severely affected, housebound patients, found no benefit at one year follow-up, reporting that 'there were no statistically significant differences in fatigue or physical functioning between patients allocated to pragmatic rehabilitation and those on treatment as usual' (Wearden 2010).

The lack of sustained long term effects of CBT (and also GET) suggests issues with placebo effects, or demand characteristics influencing initial results, especially in combination with unblinded/subjective methodology (see section 1b).

Regardless of the relative costs of delivering CBT, GET, Pacing or medications, an ineffective treatment cannot be a good use of public money.

1d Reporting of Harm

One serious concern for our community is the issue of harm caused by GET and CBT. Both anecdotal evidence and patient surveys indicate that a proportion of patients have suffered significant deterioration after GET in particular, but also after CBT. The under-reporting of harms in the GET/CBT literature is of huge concern (Kindlon 2011). Although one recent trial has attempted to ameliorate this by measuring adverse events, the way in which these harms were measured is not sufficient, in our opinion.

We feel, as has been suggested by others, that patient surveys should be given more weight by NICE (Laws 2017). Greaves et al. (2012) found that patient surveys do usually correlate well with conventional research outputs, so the discrepancy here does not automatically place the bias on patient survey sampling. The psychosocial trials also involve volunteer sample bias; this is not unique to patient surveys, and trials such as PACE are biased towards the mild end of the disease spectrum (and a likelihood of miscategorising psychiatric illness as

CFS/ME due to a loose case definition, see 1a). Also “more than half of the ‘RCTs’ in the Cochrane review failed to describe randomisation procedures, thus similarly making it impossible to assess the extent to which selection bias may have occurred” (Laws, 2017).

This table from Kindlon (2011) illustrates the scale of the issue:

Table 2. Pooled Data of Harms from GET, CBT and Pacing reported in Surveys

Therapy	Sample Size	Harms[a] (N)	Mean rate of harms (%)	Range
Graded Exercise Therapy (GET) (or similar terms)[b]	4338	2223	51.24%	28.1 - 82%
Cognitive Behavioural Therapy (CBT)[c]	1808	360	19.91%	7.1 - 38%
Pacing (or similar terms)[d]	5894	152	2.58%	0.2 - 9.3%

[a]This includes any degree of harm e.g. both *"somewhat worse"* and *"a lot worse"* from the ME Association survey [85].
[b]Taken from [75,78-80,82-85]; [c]Taken from [80,81,83-85]; [d]Taken from [79,80,83-85]

Patient surveys indicate that deterioration can be substantial with “21% more patients reporting being more severely afflicted after GET”, for example their illness going from moderate to severe (Geraghty, forthcoming). In real life terms this is experienced as long term relapse (including becoming housebound, bedbound or starting to need a wheelchair) and the risk is intolerable in the face of so little potential benefit.

> "CBT and GET with one of the leading proponents of the treatment landed me in a hospital bed, physically iller than I had ever been and psychologically scarred. [Over 20] years later I am still severely affected by ME.” (Patient voice 1)

There is a substantial discrepancy between the reporting of harm in clinical trials and deterioration in patient surveys. At the very least, this calls into question the reporting of harm during the relevant clinical trials. There may be issues with participants blaming themselves as dysfunctional if they experience harm with CBT/GET, due to the nature of the content (Kindlon, 2017; Geraghty, forthcoming), as well as more standard therapeutic relationship issues. Participants may prefer to drop out rather than report harm. Participant drop out rate is 50% higher for CBT than usual care, perhaps indicating psychological distress or physical harm (Laws, 2017). There is also some indication that participants of such trials do not actually increase activity, they fail to comply, but there is usually no objective measure of adherence in these trials to show this (Kindlon, 2017 and Helmfrid, 2016).

We request that this issue of harm reporting is more thoroughly investigated rather than dismissing patient reports.

1e Biomedical evidence and exercise induced harm

This table from an overview of the Canadian Consensus Criteria shows how the nature of our response to exercise can often be in the opposite direction to healthy controls:

Response to Exercise	Healthy People	ME/CFS Patients
Sense of well-being	Invigorating, anti-depressant effect	Feel malaise, fatigue and worsening of symptoms[1,12]
Resting heart rate	Normal	Elevated[13,14]
Heart rate at maximum workload	Elevated	Reduced heart rate[13,14]
Maximum oxygen uptake	Elevated	Approximately ½ of sedentary controls[13]
Age-predicted target heart rate	Can achieve it	Often cannot achieve it and should not be forced[13,14]
Cardiac output	Increased	Sub-optimal level[13,14]
Cerebral blood flow	Increased	Decreased[15,16]
Cerebral oxygen	Increased	Decreased[15]
Body temperature	Increased	Decreased[17]
Respiration	Increased	Breathing irregularities: shortness of breath[17], shallow breathing
Cognitive processing	Normal, more alert	Impaired[18]
Recovery period	Short	Often 24 hours but can last days or weeks[1,12,19]
Oxygen delivery to the muscles	Increased	Impaired[13]
Gait kinematics	Normal	Gait abnormalities[20]

Table from an Invest in ME overview of the Canadian Consensus

A recent meta-synthesis found that acute exercise increased fatigue over 7 relevant clinical trials, particularly after 4 hours (Loy et al, 2016).

“Acute exercise exacerbated symptoms, impaired cognitive performance and affected brain function in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome patients. These converging results, linking symptom exacerbation with brain function, provide objective evidence of the detrimental neurophysiological effects of post-exertion malaise.” (Cook et al 2017)

However, this does not just apply to intense, acute exercise, there are also problems with low-level exercise. “Bioenergetic muscle dysfunction is evident in CFS/ME, with a tendency towards an over utilisation of the lactate dehydrogenase pathway following low-level exercise, in addition to slowed acid clearance after exercise.” (Rutherford et al 2016)

Biological abnormalities lie behind our difficulty with exercise. This is likely to be why we experience harm after exercise, and combined with the complementary consistent evidence of deterioration in patient surveys, is good reason to end graded exercise as viable ‘treatment’ for ME. Please see more evidence of this in under our comments 3b.

1f There is no clear evidence that rest should be discouraged

We disagree with the current wording of CG53 where warnings about rest are given (section 1.4.2.4). There is no evidence demonstrating rest is harmful for people with ME. From our lived experience, proper rest is often the most beneficial activity. “Patient survey data consistently indicate that rest makes just 1 per cent of patients worse and is helpful to more than 85 per cent of patients” (Action for ME, 2008: 13; Action for ME, 2014: 19; Action for ME, 2001 cited in 2008: 13 which was then cited in Kirke 2017). It is therefore confusing to be given warnings of rest, but not warnings about GET.

We are particularly concerned about the lack of evidence for guidelines relating to Severe ME (eg 1.9.3.1, 1.6.2.22). Very little research has been done into patients with severe ME (Strassheim et al 2017). We are alarmed at the recommendations for "Graded activity” (section 1.9.3) given there is no evidence that this is beneficial and has the potential to cause harm and permanent bodily damage to patients with ME. The FINE trial found this type of intervention to be unsuccessful.

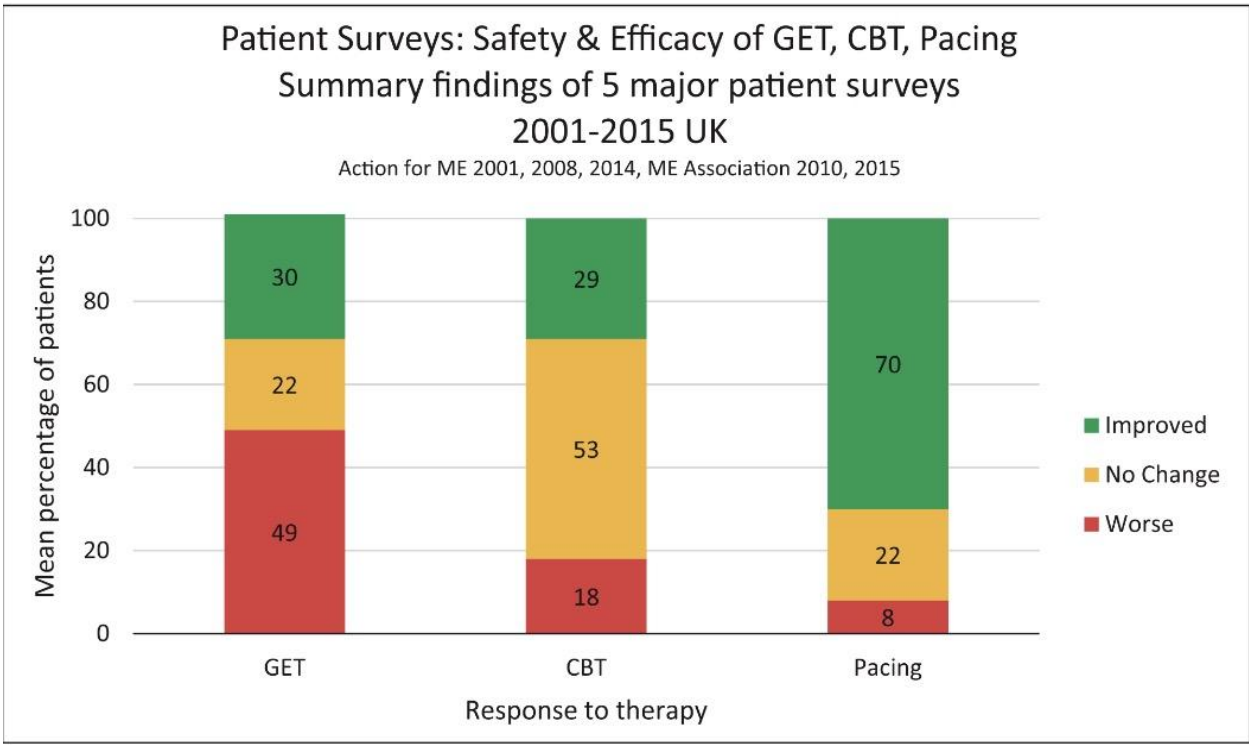
There is an urgent need for updated recommendations for the severely affected.

1g Patient preferences

It is important that any treatment recommended in the new guidelines combines: acceptance and tolerance by patients; efficacy; consistency with the evidence base; and sound theoretical underpinnings (e.g. Laws, 2017). In all of these areas we have a clear preference for Pacing (Kirke, 2017) and Energy Envelope Theory (Jason et al 2013) above the GET/CBT paradigm treatments. Patient surveys report these techniques to be more beneficial and less likely to be associated with deterioration than CBT/GET.

A forthcoming analysis examines over 18,000 patient responses to surveys on management of ME symptoms from 2000-2015: Pacing showed the largest improvement at 82% and was also the most frequently used technique (n=8762). CBT was most likely to result in no change (47% no change, total n=3251). GET was most likely to result in deterioration (57%, total n=4652) (Geraghty, forthcoming).

The same pattern is illustrated in this figure (Kirke, 2017 Figure 1)



. Summary of patient survey evidence on safety and efficacy of GET, CBT and pacing

Pacing is an adaptable approach that is able to encompass almost all levels of severity, apart from the most severe (Geraghty, forthcoming). It encourages us to stay within our current activity limits which can be achieved without triggering delayed PEM (see also Jason et al, 2013 on the Energy Envelope Theory). We have a ceiling of possible activity, depending on the current severity of our biological limitations. Under Pacing, we can sometimes increase

activity, if our underlying health improves.

Pacing “is overwhelmingly favoured by patients (84% finding it appropriate/partly appropriate) and has a moderate impact on reducing the degree of illness severity.” (Geraghty, forthcoming). Our preference for Pacing is not just based on our lived experience of this being the ‘best fit’ activity management. It also complements the research evidence that our energy is limited at a cellular level and exertion causes us unusual biological problems (Cook et al, 2017, Rutherford et al, 2016; Naviaux, 2016; Twisk, 2015; Vermeulen 2014; Nacul, 2011; VanNess, 2010; Light 2009 see Q3) because it respects these limits rather than ignoring them.

In a small study, 82% of patients improved with Pacing and the improvement was sustained at 12 months follow up (Goudsmit et al 2009), in direct contrast with PACE CBT/GET in which 80% did not improve and long term follow up was null. It should be noted that ‘Adaptive Pacing Therapy’, as assessed within the PACE trial, was not the self management ‘pacing’ as it is understood by most patients, but was an operationalised therapy designed to fit within the therapist reliant design of the PACE trial (Jason, 2017).

1h Causal CBT Model refuted

The theoretical basis of CBT and GET as treatment for ME has effectively been refuted. For NICE to fail to hold a full review at this time would demonstrate dismissal of the scientific method, which is an essential foundation for evidence-based medicine. The empirical principle is also a feature within CBT itself, for economic and ethical reasons, the CBT ethos states that treatment should be both effective and founded on well-established theories.

Whilst CG53 does not explicitly attribute any causal mechanism for CFS and ME, the main recommended treatment regimes of CBT and GET themselves necessarily imply that NICE supports the model that the illness is caused by illness beliefs and de-conditioning known as the CBT Model. It is important to understand that Cognitive Behaviour Therapy is not one monolithic structure but includes within it different approaches, models and disagreements (Westbrook, 2006). The regimes of CBT/GET used in most treatment trials for ME are not generic but are explicitly founded on these premises, which is known as the CBT Model of CFS/ME:

"The interventions with cognitive behavioral therapy and graded exercise therapy are based on a hypothesis that the disease is perpetuated by avoidance behavior and that symptoms are caused by a lack of fitness. Although the Oxford school [CBT Model, PACE trial proponent researchers] have not described any underlying mechanisms, nor presented any evidence for the presumed causation, they refer to their hypotheses either as theories or models. This gives the impression of scientific support, which in fact does not exist." (Helmfrid, 2016)

However, it is possible to imagine how this specific theoretical hypothesis can be effectively be refuted, so it is testable and falsifiable under the established Scientific Method (e.g. Popper 1963). Falsification would involve demonstrating that physical dysfunction in ME is not related to deconditioning; illness beliefs are not associated with activity levels and the treatments resulting from the model are ineffective or harmful. A competing model should also ideally be shown to better fit the data. We can demonstrate that each of these conditions apply:

1h.i **Deconditioning**: studies such as Vermeulen (2014) show that the problem in ME is not deconditioning. "The high increase of the cardiac output relative to the increase of oxygen uptake argues against deconditioning as a cause for physical impairment in these patients." (Vermeulen, 2014). Various 2-day CPET studies show a peculiar second day response, evidencing PEM (Institute of Medicine, 2015) rather than deconditioning. Many biomedical studies evidence bioenergetic difficulties incompatible with the concept of deconditioning as the cause (see 1e and 2b). Also, people who are deconditioned (perhaps from hospital admission) do not describe the experience of ME.

1h.ii Illness beliefs: a very recent study of 990 participants (defined under several case definitions) found that the theory did not fit the data, and was an especially poor fit for those who met more stringent case definitions (Sunnquist 2016, and under review, which also

supports the findings of Song and Jason, 2005). The Sunnquist study concludes:

"Findings suggest that individuals' activity level is unrelated to perceptions about illness etiology; rather, activity level is an indicator of general illness severity, along with impairment and fatigue. These findings are inconsistent with cognitive behavioral theories of [ME and] CFS that presume that individuals' symptoms stem from deconditioning and maladaptive illness beliefs. As these theories lack empirical support, and patients continue to express concerns about the efficacy of cognitive behavioral and graded exercise treatments, caution should be exercised in prescribing these treatments to patients. Furthermore, future research efforts may better serve individuals with ME and CFS by working toward developing alternative treatments." (Sunnquist 2016 p48)

There are other failures of explanation such as:
"The hypotheses do not explain why some pathogens do not trigger ME/CFS. The same perpetuating cognitive factors should be present after any infection." (Helmfrid, 2016)

1h.iii **Efficacy of treatments:** as we've demonstrated more extensively in sections 1b, 1c, 1d, and 1e, the treatments proceeding from the CBT Model hypothesis of ME do not lead to successful outcomes in trials (results are null or show unconvincingly small effects). Most patients do not benefit and a sizeable proportion deteriorate after these treatments.

There is also a lack of face validity to the treatments coming out of this hypothesis, which is perhaps explained by the irrelevance of the theory. It is widespread patient opinion that CBT and GET as 'treatments' for ME contrast sharply with our lived experience of what helps or hinders our disease. It misses something important of the essence of what it is like to live with ME. For patients this was recently encapsulated by activity diaries in the GETSET trial patient guide which were atypical, unusually mild and did not show normal PEM timing[2]. There is also a potentially biased affiliation of this hypothesis to a political agenda associated with disability and return to work, which is perhaps not in patients' best interests (Faulkner, 2016).

1h.iv **Competing model supported**:

The competing biomedical model of ME is a better fit for the data and accepted by the World Health Organisation. Although we accept that more research is needed in this area, the biomedical research fits together in a way that the causal CBT Model does not. Examples of this are presented throughout this document (see 2b and 3b). For example, in the past year several studies have agreed that there is an hypometabolic issue (see 3b ii). Although we do not yet know the results of the blinded rituximab trials (expected this year) previous results were impressive and, with the delayed benefit shown, point to an an immunological defect (see 2ai 3b.iii) This does not contradict the hypometabolic hypothesis and is complementary to it. The pieces of evidence for the biomedical jigsaw are coming together rapidly.

[2] http://www.wolfson.qmul.ac.uk/images/pdfs/getset/GET%20guide%20booklet%20version%201%2022062010.pdf

Therefore, we consider the CBT model hypothesis about the nature of ME to have been falsified under the standard procedures of normal science (Popper, 1963). This is a fundamental issue in regards to the principle of scientific rigour which NICE supports. We ask that NICE update the related treatment guidelines for CBT and GET accordingly.

1i Requests for updates:

People with ME have no confidence that CBT and GET are either safe or effective as treatment for ME.

- We ask that CBT based on the causal CBT Model for CFS and ME is excluded from the guidelines (see 1b, 1c and 1h). Generic talking therapies to process the adversity of chronic illness are acceptable to patients, but given the background context, the difference should be made explicit in the new guidelines.

- We hope that PEM as a mandatory symptom will be seen as a normal expectation for research and resulting guidelines in the future. For this review, we ask that evidence is disregarded if it combines the flaws of not including PEM in the case definition, unblinded randomisation and subjective outputs, and any studies using the discredited Oxford criteria.

- Mild ME: Following the 2015 case Montgomery v Lanarkshire Health Board the law now requires that “reasonable care to ensure that the patient is aware of any material risks involved in any recommended treatment, and of any reasonable alternative or variant treatments" . If GET is not removed from the guidelines for people with mild ME, then we feel that there must be a warning to ensure that patients are aware of the risks as per 2015 law. It is the strong opinion of patients informed of the evidence and debate that other reasonable patients who are not yet informed (perhaps due to new diagnosis) would be likely to attach significance to the risk of deterioration from recommendation to exercise as treatment for ME.

- Moderate ME: Recommendations of graded exercise (section 1.6.2.13) (or graded activity) should be suspended until concerns about methodological flaws in clinical trials and concern for patient safety have been more adequately addressed. An urgent update is necessary to avoid unnecessary, long term harm.

- Severe ME: We also ask that the unsuitability of GET for Severe ME is strongly emphasised in updated guidelines. It is the experience of patients that even those with Severe ME can be under pressure to comply with GET. We have similar concerns about the use of Graded Activity for Severe ME and wish to see the lack of evidence for this reconsidered and warnings about rest removed. Any recommendations for "Graded activity" or activity management (section 1.9.3.1) should be revised, given

that so little is known about Severe ME and the potential for these treatments to cause harm. We ask that you consult with charities such as Stonebird and 25% Severe ME who are experts in caring for people with severe ME and revise the guidelines according to their recommendations.

Question 2 Do you agree with the proposal to remove the guideline from the static list? **Yes**

We agree with the proposal to move the guidelines from the static to active list. However, the research issues we raised in 1a and 1b also apply to the FITNET trial and Cochrane review mentioned in the Surveillance review, and should be taken into account when these are published.

Due to UK research funding not being commensurate with the disease burden, we ask that NICE be open to all international, well-designed studies. This is an advancing and expanding area of research, despite a dearth of funding. There is a lot of interesting research going on into ME and CFS, including research which might lead to potential biomarkers or treatment for patients. There are currently 20 active clinical studies related to ME and CFS in the clinicaltrials.gov registry and 10 in the EU Clinical Trials register. Below we have highlighted a number of upcoming studies that we would like NICE to consider. It is essential that the guidelines are moved to the active list and updated in light of the findings of these studies.

2a Upcoming research into treatment and biomarker

2a.i Rituximab (RituxME trial)

Consultant Øystein Fluge and Professor Olav Mella at the Department of Oncology and Medical Physics at Haukeland University Hospital in Norway are researching whether B-lymphocyte depletion can be effective in ME treatment. Currently, Fluge and Mella are running a national, randomized, double-blinded and placebo-controlled multicentre phase III study with the monoclonal antibody Rituximab on patients with ME. The estimated completion date of the trial is September 2017. Rituximab is a monoclonal anti-CD20 antibody and is a licensed product for non-Hodgkins Lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis and granulomatosis. It has been shown to effectively deplete B-lymphocytes in rheumatoid arthritis and non-Hodgkins Lymphoma (reviewed in Donner, 2010). Fluge and Mella have conducted several human trials investigating the effect of Rituximab on patients with ME. These studies found that in a subset of patients, fatigue scores improved following 6-10 months of treatment. Three studies on Rituximab clinical trials in ME patients have been published (Fluge and Mella 2009, 2011, 2105). In addition to supporting the potential use of Rituximab to treat ME, these findings suggest a possible role for B cells in ME. Further work by researchers at University College London has shown that ME is indeed associated with an altered B cell phenotype (Mensah et al 2016). Fluge and Mella present the hypothesis that the delayed response to treatment suggests that ME is an autoimmune disease and that autoantibodies may be gradually removed preceding a clinical response (Fluge and Mella 2011).

ME Research UK has funded research looking into a way to predict which ME patients will benefit from Rituximab, by looking at immune signatures. This work is being conducted Professor David Patrick at the School of population and Public Health, University of British Columbia, in collaboration with Drs. Fluge and Mella.

Currently, the UK charity Invest in ME is funding an ongoing Rituximab clinical trial in the UK, at University College London, where the principal investigator is Dr. Jo Cambridge. The charity is being advised on the trial by Professor Jonathan Edwards, one of the pioneers of the use of Rituximab in rheumatoid arthritis at University College London. Consultant Øystein Fluge and Professor Olav Mella are also collaborators on the trial.

2a.ii Cyclophosphamide (CycloME trial)

Drs. Fluge and Mella at Haukeland University Hospital in Norway are also conducting a phase II clinical trial investigating the effect of cyclophosphamide treatment in patients with moderate to severe ME. Cyclophosphamide is a DNA replication inhibitor used to treat cancer and autoimmune diseases. **The trial completion date is July 2017 (ClinicalTrials.gov).**

2a.iii Immunoglobulin therapy

Immunoglobulin therapy is an effective treatment in a number of diseases including primary immunodeficiency, autoimmune diseases and HIV/AIDS. Charité Universitätsmedizin Berlin is

currently running a proof of concept study in 15 patients to assess the effect of subcutaneous immunoglobulin infusions (HyQvia formulation from Shire Pharmaceuticals) on patients with ME/CFS. **This study is estimated to be completed in 2018 (EU Clinical Trials register).** Studies in the 1990s reported mixed results; however, patient definitions were redefined in 2015 and further research is warranted. This treatment is not widely available to ME patients in the UK.

2a.iv Ongoing biomarker studies

We feel these studies are important to NICE as they may identify biomarkers and diagnostic tests which would be important for updating section 1.3 of the guidelines. Recent work identified activin B as a novel serum biomarker for ME/CFS (Lidbury 2017), and numerous studies have identified immunological disturbances that are potential biomarkers (e.g. (Brenu 2011)). In addition, there are at least a couple of these studies ongoing at the moment:

- The National Center for Neuroimmunology and Emerging Disease at Griffith University in Australia were recently awarded a grant from the Stafford Fox Foundation for biomarker discovery in ME/CFS. They aim to produce a diagnostic test for ME/CFS by 2021 (Griffith University 2017).
- The Open Medicine Foundation is running a collaborative biomarker discovery project (ME Severely Ill Big Data Study) focused on severely ill patients, involving a wide spectrum of high throughput approaches (combining proteomics, RNA sequencing, metabolomics), clinical tests and monitoring (Open Medicine Foundation 2017).

2b Funded research projects on ME/CFS by funding body

We have included this section to highlight that most national and international researchers, from a variety of medical disciplines, do not agree with the causal CBT Model or with using CBT/GET as a treatment (see 1h). These researchers are all investigating other causes and treatments and we feel the guidelines should take into account their recent and ongoing work. The future research highlighted in the 10 year surveillance systematic review exclusively supported the causal CBT model of ME, which is popular with a few UK proponents but is not supported by biomedical evidence (see 1h). We also feel that NICE should keep up to date with research looking into the cause of ME, as this is relevant to assessing the relevance of treatments.

2b.i UK Medical Research Council

The MRC are funding a number of biomedical research projects on ME. Highlights include: Professor Anne McArdle at the University of Liverpool was the recipient of a grant to study the function of mitochondria and cytokine production in the skeletal muscle of patients with ME/CFS; Professor Julia Newton at Newcastle University was granted funding to investigate the pathogenesis of dysfunction of the autonomic system in ME/CFS and how this relates to cognitive impairment. In addition, Dr Carmine Pariante at King's College London has received funding to establish an immunological model for ME and CFS.

2b.ii NIH

There are 43 active grants in the NIH reporter supporting biomedical research into ME. The NIH in the United States is currently conducting an exploratory cross-sectional intramural study to learn more about the cause of ME/CFS, **estimated to be completed in September 2018 (ClinicalTrials.gov).** Following a workshop on ME, NIH issued a call to action in 2015 for increased research effort. Proposals for a recent NIH funding opportunity are currently under review and will result in three new ME/CFS Collaborative Research Centers as well as a Data Management and Management Center. The NIH also issued 7 supplemental grants to expand ME research in existing grants.

2b.iii Research Council of Norway

The Research Council of Norway has awarded funding to several researchers for biomedical research into ME/CFS (Forskningsgradet.no). Of particular note, the University of Oslo received funding for genetic studies in ME to investigate the potential involvement of the immune system and reveal biomarkers. The University of Bergen was awarded a grant for study of defective energy metabolism in ME/CFS, and the University Hospital of North Norway, Harstad, was granted funding for research into fecal microbiota transplants in ME/CFS.

2b.iv Solve ME/CFS

Solve ME/CFS is currently funding several seed projects related to ME/CFS. Their research includes looking into possible viral causes, exercise physiology, immunology and neuro-

imaging. They are also funding research into repurposing drugs which have been shelved or are used for other diseases. These drugs have already passed a significant number of safety tests ensuring they are safe. This should significantly reduce the time it takes for them to be available, if they prove beneficial to ME patients.

2b.v UK ME/CFS Biobank

The UK ME/CFS Biobank was established at the London School of Tropical Medicine and Hygiene in 2011 (Lacerda et al 2017). A large dataset of clinical samples has been obtained to enable comprehensive phenotyping of ME/CFS patients.

In conclusion, we agree with the decision to remove the guidelines from the static to active list. However, we are concerned about the emphasis on updating the guidelines purely on the basis of UK psychiatric research, especially since this is based on a refuted model and treatment that has caused widespread harm to patients. Both nationally and internationally, exciting research is being done into the cause and potential treatment of ME, in a variety of academic disciplines. It is of utmost importance that this research is considered in any future update.

Q3 Do you have any comments on areas excluded from the scope of the guideline? **Yes**

We consider there to be a number of omissions in the guidelines. We summarise a few of the main omissions below and would welcome the opportunity to explore this issue fully when there is a full review of the guidelines.

3a Key Omissions

3a.i POTS and Orthostatic Intolerance

Postural Orthostatic Tachycardia Syndrome is a common comorbidity with ME and CFS, as has been shown in recent research. Okamoto et al (2012) found the majority of POTS participants also had CFS symptoms. About a third of people with ME meet POTS diagnostic criteria (Hoad et al, 2008). It could be the case that there is a common cause, as both conditions show similar issues with autoantibodies (Loebel et al, 2016), as yet this is uncertain, but it is established that a substantial comorbidity exists. “The presence of POTS marks a distinct clinical group of CFS patents, with phenotypic features differentiating them from those without POTS.” (Lewis et al, 2013).

Many patients miss a useful diagnosis of POTS for years because tests for POTS and other Orthostatic Intolerance issues are not recommended by the NICE guidelines at the point of ME diagnosis (section 1.3) . This needs to be revised.

POTS has a number of reasonably effective treatments which could be used for patients with ME in this phenotype group. These include increasing salt, compression tights, off label drugs such as beta blockers, ivabradine, midodrine, fludrocortisone. An approach to this is covered well in the recent Paediatric Primer (Rowe et al, 2017). We ask that the guideline’s section 1.4 be updated to suggest these as potential treatments.

3a.ii Gut dysbiosis

Intestinal dysfunction is a common symptom of ME, and up to 90% of patients report abdominal discomfort. Recent publications have identified shifts in the gut microbiota in people with ME compared to healthy controls (Fremont 2013), and further work has identified reduced microbial diversity in patients with ME compared to controls (Giloteaux L et al 2016, Nagy-Szakai D et al 2017). Following exercise, the gut microbiota of ME patients is also altered (Shukla SK et al 2015), implicating the gut microbiome in worsening of symptoms following exercise, a major feature of ME presentation. There is evidence for increased translocation of intestinal bacteria to the blood in these patients review by (Morris G et al 2016) which may be a source of inflammation in ME. These studies have led to ongoing research investigating the impact of faecal transplants on ME/CFS symptoms.

Given the prominence of gut dysfunction in ME, we ask that further advice for this is given (rather than the brief mention of exclusion diets in section 1.4.1.5 of the guidelines).

3b. Recent Important Areas of International Research

In this section we have included recent research from international researchers which we feel are relevant to any decision made on the care and treatment of people with ME. We feel that the conclusions of recent and influential publications such as the The Institute of Medicine (IOM) report [(now The National Academy of Medicine, NAM)] of the National Academy of

Science (US) published in 2015 should be not be so easily dismissed by the reviewers: it details over 9000 articles related to ME/CFS and is the most comprehensive review to date.

3b.i ME as a neurological disease

A large number of publications have identified distinct neurological changes observed in patients with ME. Grey matter is reduced in patients with ME/CFS (de Lange FP et al 2005). In 2015, brain images of patients with ME/CFS identified numerous differences in brain structure compared to healthy controls (Zeineh et al 2015). Natelson et al surveyed brain and spinal fluid in patients with ME/CFS, with or without psychiatric comorbidity (Natelson B et al 2017). No differences in outcome between ME patients with or without psychiatric comorbidity were observed. This research provides further evidence for the presence of neurological abnormalities in ME regardless of psychiatric status. Along with numerous previous studies showing that exercise exacerbates ME symptoms, a recent study assessed patient symptoms and brain responses following exercise showed that neurophysiological symptoms in ME patients worsen as a result of physical exertion (Cook et al 2017), linking exercise to cognitive impairment in ME patients.

There are currently 88 published studies in peer-reviewed journals that demonstrate ME is a neurological disease and until the specific cause is found it would be appropriate to classify it as such. ME is classified under the diseases of the nervous system by the World Health Organisation in its International Classification of Diseases. Based on this evidence, it would be most appropriate for NICE to classify ME as a neurological condition in the guidelines. We would be happy to provide full references of these studies if required.

3b.ii Metabolic shift in ME

Survey of serum metabolites has identified shifted metabolism in patients with ME. A chemical signature of ME was identified from serum metabolites and the direction of shifted metabolism was the opposite to that of metabolic syndrome; in contrast, ME resembles a hypometabolic state (Naviaux RK et al 2016). The observation of a metabolic shift was corroborated by two further metabolomic studies (Fluge O et al 2016 and Germain A et al 2017), the former implicating insufficient ATP levels and excessive lactate production following exertion in clinical disease presentation. Increased intramuscular acidosis occurs in ME patients following physical exertion, likely due to reduced anaerobic threshold (Jones DE et al 2012). In ME patients, elevated lactate is also observed in the cerebrospinal fluid (Mathew SJ, et al 2009). Furthermore, exposing muscle cells to serum from ME patients results in defective metabolism and increased lactate production (Fluge et al 2016). Together, these findings provide a mechanistic link between energy expenditure and exacerbation of ME symptoms, thus contraindicating the use of exercise therapy (e.g. graded exercise therapy or physiotherapy) in improving ME symptoms.

3b.iii Immunological disturbances in ME

In recent work on adolescents suffering from ME, differential expression of genes related to B cell differentiation and survival was observed (Nguyen CB et al 2017). Numerous studies have

identified altered immunological responses in patients with ME. Distinct plasma and cerebrospinal fluid cytokine patterns have been observed in ME patients (Peterson D et al 2015, Hornig et al 2016), and these patterns fluctuate with illness duration (Russell L et al 2016, Hornig et al 2015; Hardcastle SL et al 2015), suggesting that ME is not a static illness. Furthermore, cytokine levels in subsets of patients associate with classical or atypical disease presentation (Hornig M et al 2017). Impaired natural killer cell function has been known to be associated with ME for over 20 years (Whiteside TL and Friberg D 1998, Ojo-Amaize EA et al 1994).

3c Treatments excluded from guidelines
We would also like the review board to consider the following evidence for treatment which has so far been excluded from the guidelines.

3c.i Ampligen / Rintatolimod
Ampligen has been approved for treatment of ME in Canada since 1997 and in 2016 was approved for people with ME in Argentina. In two clinical trials, treatment with Ampligen resulted in an increase in exercise tolerance (Strayer et al. 1994, 2012). Based on these studies, an NIH working group wrote that Ampligen may benefit patients with ME (Smith 2015). In 2016, the manufacturer established an Early Access Program for Ampligen for ME/CFS patients in the EU and Turkey.

3c.ii Valganciclovir
Valganciclovir is an antiviral drug. A randomized clinical trial demonstrated an improvement in mental fatigue score, fatigue severity and cognitive function in patients treated with valganciclovir compared to placebo (Montoya et. al 2013), following an initial encouraging prospective unblinded study (Watt et. al 2012). Anecdotal evidence suggests that this treatment is effective in a subset of patients but further research is warranted.

These are just a few of the areas which we feel are excluded from the guidelines. We identified POTS and gut dysfunction as key targets for guideline revision. We believe it to be important to include current international research in your consideration of the general nature of ME, as we think any decision into diagnosis and treatment of people with ME should be made in the light of the best available evidence.

Q4: Do you have any comments on equalities issues? **Yes**

4a Stigma and discrimination

It should be taken into account that people with ME experience a type of stigma specifically associated with this chronic illness disability. Prejudice and misunderstanding has often been spread by the British media.

We believe that several sections of the current NICE guidelines (e.g. section 1.4.5) are not entirely without merit in content, if they existed in a socio-political vacuum and were read by entirely neutral professionals. However, our healthcare professionals, DWP assessors, insurers, employers, social workers and relatives do not live in this vacuum and their actions in relation to us are influenced by the sociopolitical context of ME. Colloquially the interpretation of the NICE guidelines can be that if people with ME, including people with Severe ME, 'think positive and exercise', this is enough to for us to get better. As the evidence we have presented above indicates, this is not the case and can lead to negative outcomes. We suggest that the wording of the guidelines needs to explicitly acknowledge and guard against these misconceptions.

Evidence of this issue can be found in a 2015 survey by Action for ME of 850 respondents (sample included representative proportions of mild, moderate and severe ME), 97% met the threshold of difficulties with daily living which may entitle them to a social care package according to criteria in the Care Act 2014. Only 6% actually had a social care package and only 16% had had a social care assessment in last 5 years. The study investigated barriers to accessing the social care system and found:

- 40% of respondents indicated a reluctance to ask for help due to the stigma attached to the ME.
- 84% agreed that they were worried the assessor would not believe that they were genuinely disabled
- 84% agreed that they were worried that they wouldn't be considered deserving of help or support

Half of the respondents also offered further evidence indicating stigma was a significant factor in avoiding social care assessments. Responses included:

"The social worker said I should go swimming every week and do more exercise, even though she could see I couldn't even stand up without falling onto the floor and my legs were going into visible spasms on that day."
"I'm concerned that drawing too much attention to myself might end up with me being pressurized into having inappropriate treatment or wrongly being labelled as mentally ill when I'm not."
"I'm fed up with being judged."
"Because of the stigma with this illness, I have little confidence and the fact that it is a fluctuating illness and it is hard to make myself clear."
"The community service worker mistook my cognitive symptoms for depression or anxiety. She told my consultant that I was afraid of activities of daily living. It was recommended I see a psychiatrist and I was questioned under guidelines of Mental Health Act and I thought I was about to lose my freedom."
"The social worker told me that 'everyone gets tired'"

4b Prejudice leading to pressure to comply

Although section 1.1.1.3 of the guidelines states that patients have the right to refuse or withdraw from any component of their health care plan without affecting care or future choices about care, we do not feel this statement goes far enough to protect ME patients given our context. Patients often feel compelled to undertake treatment such as graded exercise (which, as discussed above, is inappropriate for them). As a result, patients can experience serious consequences: child protection proceedings (see input from Tymes Trust); loss of benefits; difficulties with employers and insurance providers and withdrawal of family support. The BBC Radio 4 programme 'File on 4' recently highlighted the discrimination children and their parents face when children get diagnosed with ME. The programme discussed how the stigma surrounding the disease meant children were not treated appropriately and that parents were falsely accused of child abuse due to poor understanding of symptoms, care and treatment by healthcare professionals and schools (Radio 4, 2017). The result of knowing that at least 193 families have been through this ordeal is that other parents feel pressured to comply with GET, even though they fear it will make their child worse.

Given the context of this discrimination, we ask that the updated NICE guidelines be made clearer to account for the limitations of the evidence, patient reports of long term relapse following graded exercise, and the importance of genuine patient choice without reprisal (section 1.1.1.3).

We have divided references into key references, which is the main evidence we wish to draw your attention to, and additional references

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Thank you for considering our response.