National Institute for Health and Clinical Excellence

CG53: CFS/ME
Guideline Review Consultation Comments Table
1-14 November 2010

| Stakeholder | Agree? | Comments<br>Please insert each new comment in a new row. | Comments on areas excluded from original scope | Comments on equality issues |
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| GDG member | Yes | I agree with what is stated especially with education of Health Professionals and would like to add the urgent need for biomedical research because I and many others feel that this is the only thing that can move things forward in the diagnosis and the treatment of people who are at this moment diagnosed (rightly or wrongly) with CFS/ME and are still discriminated against. The old Yuppie Flu label sticks! | | |
| Royal College of Nursing | Yes | | | |
| Royal London Hospital for Integrated Medicine (part of UCLH) | Yes | | | |
| British Nuclear Medicine Society | | | There remains no clear evidence that there is a diagnostic pattern of abnormalities that can differentiate ME/CFS from depression using SPECT or PET. | |
| Lincolnshire Teaching Primary Care Trust | Yes | | | |
| BACME British Association for | Yes | The majority of the members of BACME who responded agreed that there is no new evidence to suggest that the existing guideline should be amended. | No | None |

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| Chronic Fatigue Syndrome / ME | | The group have recommended that it would be useful for the guideline to be reviewed once the PACE trial has been published.<br><br>Comments from our members also included:<br>▪ To review the CFS/ME Guidelines once PACE have published their research because this should give very valuable information about appropriate management in the future.<br>▪ As the PACE trial is due for publication, the decision not to review needs to be suspended until this information is available as the findings could impact on current recommendations with respect to pacing as an intervention<br>▪ To include ferritin in the basic blood screening, regardless of other parameters (GP forum)<br>▪ To revise the definition of pacing as an intervention for CFS/ME (using information from Jason LA and Goudsmit EM.<br>▪ For the guidelines to include more emphasis on the multi-disciplinary approach for CFS/ME management and rehabilitation<br>▪ There is also considerable excitement recently about the potential role of a retrovirus (XMRV) in the causation of CFS and the potential that may have for antiviral treatment. It is be important to review all the data for the use of anti virals with CFS/ME and provide guidance to discourage the use of unproven approaches. This would be achieved if the guidelines were reviewed.<br>▪ Although there has been much more interest in CFS/ME recently from the biomedical research community (including the MRC) there have been relatively few good trials in this area. | | |

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| Royal College of Paediatrics and Child Health<br><br>*This comment has been amended in June 2011 at the request of the stakeholder* | Yes | The College notes that current evidence suggests there is no evidence to revise existing treatment guidelines. Results of trials in progress or trials planned may, however, lead to revisions being necessary, so the date for the next review of the guideline should not be left for more than three years.<br><br>We do not fully agree with the comment on page 5 that the FINE trial gave inconclusive results. In particular it was shown that nurse-delivered supportive listening did not give any advantages in any parameter, at any point in the trial, over usual GP care. This is an important finding as such therapies are on offer as the authors make clear. | We suggest that NICE revisit the literature in two years to see if an update is warranted at that time.<br><br>We think that a future update would need to address the issue of causality. However, this is merely academic until there is a consensus on aetiological pathways. | We note that some patients with CFS/ME feel discriminated against because they think doctors don't regard it as a 'real' illness. Such patients may experience unequal access to healthcare. Establishing a consensus about causality would greatly help with this. |
| North of England CFS Network | No | This review does not address the issues regarding diagnosis: published and unpublished data shows that 40-50% of patients referred to physicians expert in the diagnosis of fatigue-related conditions do NOT have CFS/ME. The corollaries of this are: i) it is inappropriate for GPs to refer unscreened patients directly to therapists; all services must have pathways that ensure review of ALL patients by an consultant physician experienced in the full differential diagnosis of fatigue; ii) many patients currently in CFS therapy services should not be there as they will have non CFS/ME conditions better managed elsewhere. | The importance of identifying postural orthostatic tachycardia syndrome (POTS) in association with CFS needs to be included: this is a common associated symptom that needs to be highlighted, as there are effective drug treatments available for this that will improve symptoms.<br><br>The use of mindfulness therapy in place of CBT needs to be considered.<br><br>Lightning therapy may be effective and needs to be reviewed (NLP) | The services provided are not equal in all parts of the country. Many patients are referred to therapy services without formal review by a consultant physician (see above). This means that patients with treatable conditions are being managed inappropriately. |
| University of Manchester, on behalf of the FINE Trial team | Yes | N/A | No | None |
| West Midlands | No | We do not agree with the proposed review decision. | a) A clear warning about the hazard | |

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| ME Groups Consortium [WMMEG] | | The reasons we would put forward would be:<br><br>a) The need to differentiate ME from Chronic Fatigue (Syndrome) and little meaningful progress can be made until this is reflected in separate Guidelines for each<br>b) Emerging & conflicting evidence of retroviral and viral involvement in ME – this lack of certainty should evoke caution and the NICE Guideline for CFS/ME should contain a stronger warning about exercise particularly at the acute stage of the illness and during relapses.<br>c) The Guideline should also contain a warning about the lifetime ban on blood donation by people who have been diagnosed with ME<br>d) We do not agree that the FINE trial was “inconclusive”. It stated that no long term benefit at all was accrued from either pragmatic rehabilitation or supportive listening. We think this clearly shows that biopsychosocial interventions are unhelpful (useless?) for people with ME – in general & in particular for the more severely affected patients. This should be reflected in a revised Guideline. | of exercise for many CFS/ME patients<br>b) Failure to recognise and identify subgroups and ‘treat’ appropriately. | |
| Department of Health | | No comments to make | | |
| The ME Association | | The ME Association is very disappointed to learn that feedback from various sources to the guideline review process indicates that there is no need to carry out a three year review into a document that has been very heavily criticised by specialist organisations such as the British Psychological Society, neurologists, and most of the charities that represent patients with ME/CFS.<br><br>The MEA continues to believe that the current guideline on ME/CFS is skewed towards two largely psychiatric models of | | |

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| | | ME/CFS and three interventions based on these models. We also regard the recommendations regarding management as needlessly restrictive, and submit that the definition requires amendment. Our reasons have already been communicated to NICE in our previous submissions.<br><br>Focusing on both the need to provide practitioners with clear and evidence-based information, plus the obvious aim to improve patient care, it is of vital importance that the guideline recognises the heterogeneity of clinical presentations that make up ME/CFS *and* that the advice reflects this.<br><br>Previous submissions by ourselves and others, summarised in a report to you by Dr Ellen Goudsmit FBPsS, demonstrates quite clearly that there is now sufficient, good quality evidence for alternative approaches, and given that some of the relevant trials were published in journals cited by PubMed, we find it hard to understand why this information was not recognised by your experts.<br><br>The review should also take account of the growing evidence against the two protocols for cognitive behaviour therapy (CBT) and graded exercise therapy (GET) for everyone with mild to moderate ME/CFS. If the guideline is to be based on sound science, the existing recommendations must be amended. Moreover, the recommendations can no longer dismiss the consistent evidence from patients, obtained from surveys here in the UK (e.g The ME Association Management Report which contained feedback from over 4,000 respondents: http://www.meassociation.org.uk/?page_id=1345) and from the rest of the world, plus the independent audits, all of which indicate that these two forms of treatment are of limited efficacy or can even make the condition worse.<br><br>We are therefore calling for the guideline to be reviewed, and as set out in the points below we believe there is compelling new evidence which supports a more flexible approach involving | | |

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| | | other forms of management (i.e pacing) that are both effective and acceptable to people with this illness.<br><br>1 The information on pacing in the current guideline is inaccurate and vague (e.g what does balancing rest and activity entail?). It requires a science-based definition plus practical guidance based on evidence - so that pacing can be added as an additional option for therapists. Pacing is appropriate for the vast majority of patients, but may not be suitable for everyone who comes under the CFS umbrella. NICE needs an expert view of this to guide you through the literature.<br><br>2 There needs to be a review of the multidimensional programmes which have been assessed in controlled trials (e.g. Goudsmit et al, 2009), and two RCTs (e.g. Taylor et al, Jason et al, 2007), as these appear to be safe, acceptable and as 'effective' as the CBT programmes based on the Chalder and Vercoulen protocols. The NICE recommendations as they stand are unduly restrictive and do not take into account recent evidence on outcomes, e.g. Wiborg et al 2010 (CBT/GET does not increase activity levels).<br><br>3 The FINE trial has resulted in findings that are far from 'inconclusive' (as stated on p5 in the Centre for Clinical Practice review). This assessment is open to challenge. In fact the FINE trial seemingly found that all of the arms of the trial – pragmatic rehabilitation, supportive listening or GP care - resulted in limited or no statistically significant benefit for patients. This sheds considerable doubt on the effectiveness of managing ME/CFS in primary care, and must have implications for the future research agenda for ME/CFS. This is within the scope of the full NICE guideline.<br><br>We would also draw your attention to the literature on the CDC guidelines, which has attempted to address the flaws and which | | |

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| | | is therefore a significant improvement on earlier case definitions - as it reduces heterogeneity and therefore adds to diagnostic precision. We are sure that NICE is keen to promote the latter and thus increase the likelihood of better management and a reduction in the severity of ME/CFS. The latest paper on the revised Canadian criteria covers the inadequacies of earlier diagnostic criteria well and deserves serious consideration.<br><br>Finally, we note that NICE has not responded to new evidence of pathology related to post-exertional malaise, and we therefore feel that it would be hard to justify a blanket recommendation of the GET protocols that are currently described. GET may help some individuals, but equally, it makes others worse.<br><br>If the NICE guideline on ME/CFS is to be based on best evidence and rigour, then certain changes must be made.<br><br>The MEA is most disappointed with the document you sent us that was prepared by the Centre for Clinical Practice but we hope that we can engage in a constructive discussion to help not only those who manage patients with ME/CFS, but also the patients themselves.<br><br>We therefore urge you to reconsider the advice you are being given. | | |
| Action for M.E. | | Action for M.E. is greatly concerned that there has long existed a discrepancy between evidence from comparative trials of the efficacy of physical rehabilitation therapies and accounts from patient groups and organisations. This is true above all in relation to the two treatments recommended by NICE for M.E.: Graded exercise therapy (GET) and Cognitive behavioural therapy (CBT). The treatments currently recommended are at best coping strategies, at worst make symptoms worse, and for many have no lasting benefits at all. A 2008 patient survey by Action for M.E. indicated that 34% of respondents reported having been made worse by GET, 21% reported no change, and | We would suggest that rather than consider only whether new data contradicts any existing recommendations, it is important to consider also whether any new material, might enable the guideline to be updated. This applies both to studies which would not usually be viewed to have a direct implication for management such, as studies which suggest that MLV-related | |

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| | | only 45% found it helpful. The same survey indicated that CBT had been helpful to only 50% respondents, with 38% reporting no change and 12% made worse.<br><br>This highlights the case to incorporate a broader cross section of approaches until it has been determined why some treatments work for one patient, and not for another. We would also recommend that the revised guideline includes a statement that many patients have reported that graded exercise has made their symptoms worse. This advice has been incorporated into NHS Scotland's Good Practice Statement for M.E./CFS which emphasises a patient centred approach.<br><br>Pacing has long been reported as the most effective management strategy by M.E. patients. It is not therefore clear why the review decision is being taken before the imminent dissemination of the findings of the PACE Trial.<br><br>Action for M.E. supports the need to ensure that any treatment made available to patients is safe and efficacious. On these grounds and in these exceptional circumstances we would urge NICE to reconsider the emphasis placed on randomised control trials, to seek to extend its scope beyond the usual hierarchy of evidence which does not adequately represent the treatment landscape for this diverse group, and to take into account patient feedback and other research which has been published in peer review journals. | retroviruses are associated with CFS, and to data such as patient feedback which does not feature highly on NICE's hierarchy of evidence. Patient feedback is particularly significant in the case of M.E. which is so poorly understood medically, and where there is great variance in both the combinations of symptoms which patients experience, and in the efficacy of the treatments currently recommended by NICE.<br><br>We quote the views of Sir Michael Rawlins: "Randomised controlled trials (RCTs), long regarded at the 'gold standard' of evidence, have been put on an undeserved pedestal. Their appearance at the top of "hierarchies" of evidence is inappropriate; and hierarchies, themselves, are illusory tools for assessing evidence. They should be replaced by a diversity of approaches that involve analysing the totality of the evidence-base."<br><br>The following points have been submitted by people with M.E. and their supporters during our consultation with them:<br><br>• Two books have been published since guideline 53 was issued that might be worth considering to see if the guideline could be | |

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| | | | strengthened in the area of pragmatic management of symptoms in mild, moderate and severe cases: Fighting Fatigue by Pemberton and Berry, and Severe ME/CFS: A Guide to Living by Collingridge. These resources could be said to embody a clinical consensus on management techniques, in areas where robust scientific evidence may be lacking, and as such, it would be desirable for NICE to consider them.<br><br>• Although the findings of the FINE trial have been deemed 'inconclusive' (page 5), it is noted that the FINE trial seemingly found that all of the arms of the trial – pragmatic rehabilitation, supportive listening or GP care - resulted in limited or no statistically significant benefit for patients. This may shed doubt on the effectiveness of managing CFS/ME in primary care, and must have implications for the future research agenda for CFS/ME.<br><br>• Brain studies in CFS/ME | |

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| | | | subjects: see the Gudrun Lange review: Brain Pathology in CFS/ME for an overview of some of the research in this field.<br><br>• The existing assessment of evidence is open to criticism since it is based on the 2006 York Review. Flaws in this review have since been identified.<br>e.g. the Powell papers of 2001 and 2004 were given a rating of 17 out of 20, despite the fact that patients were selected using the Oxford Criteria (too broad to be applied to CFS patients as currently understood via the Canadian and CDC/Fukuda definitions), there was a high drop-out rate in the 2001 treatment group, lack of objective medical criteria to support statements, etc. The weaknesses of the 2001 paper have been well documented in the pages of the BMJ. | |
| East Anglia ME Patient Partnership (EAME) | No | Response posted separately at the end of the document as too large for the table | | |

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| 25% ME Group | No | Response posted separately at the end of the document as too large for the table | | |
| The Young ME Sufferers Trust | No | There are two new research papers that provide new evidence which we feel have important implications for the existing NICE treatment recommendations.<br><br>The first is *Biomedical and Vascular Aspects of Pediatric Chronic Fatigue Syndrome* by Gwen Kennedy et al, Arch Pediatr Adolesc Med. 2010;164(9):817-823). This showed that 'biomedical anomalies seen in adults with CFS/ME – increased oxidative stress and increased white blood cell apoptosis – can also be observed in children with clinically diagnosed CFS/ME compared with matched controls'.<br><br>The conclusion of the research team was that these children showed evidence of persistent viral infection. Although the remit of NICE does not include aetiology, if aetiological discoveries have relevance for treatment we believe that such discoveries must be taken account of by NICE.<br><br>This discovery could have great relevance for graded exercise therapy and could well explain why patients commonly report being made worse by exercise during their long recovery process. There is plenty of evidence from patients to show that those who are not treated with graded exercise make good recoveries over time, as in any other viral illness for which there is as yet no antiviral treatment.<br><br>The second paper is 'Close analysis of a large published cohort trial into fatigue syndromes and mood disorders that occur after documented viral infection' by D.P. Sampson, Bulletin of the IACFS/ME, which reanalysed data used by Professor PD White in his *Lancet* study upon which much of the deconditioning theory of ME/CFS appears to have been based.<br><br>Sampson argues that Professor White's conclusions are not | In the Dept of Health Report 2002, there were some very helpful comments about the fact that children with ME/CFS may require education in the home for quite some time. Doctors need to be informed that there are 21st century educational options eg interactive virtual education, which have proven their worth in terms of the child's recovery from ME/CFS, and which are commonly provided by Local Education Authorities (LEAs) WHERE THIS HAS BEEN REQUESTED/RECOMMENDED.<br><br>We are not suggesting that NICE should recommend one sort of education over another, because that is clearly a matter for educationists and is outside the remit of NICE. However, it is not sufficient simply to advise doctors to liaise with schools and LEAs, as doctors are commonly unaware that there are effective options other than school. It is important to bring alternative forms of education which are energy-efficient to the attention of doctors managing cases of ME/CFS.<br><br>GPs and paediatricians need to know that there are other choices available to help their young patients. Such | The issue of the rights of children with disabilities is not sufficiently addressed. At the moment they commonly suffer discrimination.<br><br>It should be made clear that children with ME/CFS may require wheelchair assistance, for example. In school they may need assistance with carrying bags, facilities to study on the ground floor, or to use lifts.<br><br>Doctors often refuse to endorse requests for a wheelchair when they believe that ME/CFS is a psychological condition or believe that there are psychological issues which perpetuate the illness. They say things like 'once in a wheelchair never out', or simply state that having a wheelchair will prolong the illness. There is no evidence for this, and anecdotal evidence is overwhelmingly to the contrary. |

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| | | supported by the evidence in his study. If this is indeed the case, then the theory upon which graded exercise treatment is based may be flawed, which could have profound implications for NICE treatment recommendations. | options have a track record of producing good educational qualifications for the children, and evidence from Local Education Authorities shows that the children are often able to return to school as their health improves. | |
| Carers together | No | For the reasons listed below , I am greatly concerned that Clinical Area 1, case definition, concludes that "no conclusive evidence was identified that would invalidate current guideline recommendations. " that Clinical Area 3, management, concludes that : "There is currently no new published evidence that would invalidate current guideline recommendations ."<br><br>• the competing interests of the original GDG members were undeclared,<br>• the patients to whom the Guideline is meant to apply were not defined: the Guideline does not describe or distinguish the neurological disorder ME/CFS from "medically unexplained chronic fatigue" (a classified somatoform disorder)<br>• patients were sent the Evidence Review, a massive 487 page document, only four weeks before receiving the Questionnaire on April 7th 2006,which had to be returned by May 5th.<br>• the Questionnaire only concerned itself with 18% of the | | |

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| | | issues under discussion, so the consultative process did not involve the full range of relevant issues. Misleading instructions to questions 29-61 made it likely that answers to those questions were erroneous. Out of a probable ME population of 240 000 patients, only 219 responses to the Questionnaire were considered, of which only 119 were from patients.<br>• NICE failed to include experts from all the relevant professional groups on the Guideline Development Group.<br>• Patients' / carers' views were not given equal weighting and status, as subsequently confirmed by two members of the GDG<br>• NICE entirely failed to heed the submitted evidence and disregarded the published dangers of GET for patients with ME/CFS who have cardiovascular and respiratory problems.<br>• By limiting their consideration of the literature to that which supports the psychiatric paradigm of ME/CFS, NICE exhibited intrinsic psychiatric bias and failure to take account of the available published biomedical evidence about ME/CFS (over 5000 papers), without knowledge of which the Guideline fails to provide an aid to diagnosis (as was its remit). | | |

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| | | • The sole management recommendations are based on weak and inconclusive studies of dubious quality on heterogeneous groups of people, the majority of whom are unlikely to have ME but may have suffered from any one of over 30 other disorders where "fatigue" is a symptom.<br>• The guideline was not based on a full and true picture of the severity of the illness and symptoms and itself concedes that its management strategy cannot be recommended either for the severely affected or for children.<br>• The Guideline's conclusions did not coincide with the majority professional view of the international medical and scientific communities about ME/CFS.<br>• The Guideline compromised the reality of ME/CFS by remaining irrationally equivocal about the WHO classification of ME/CFS as a neurological disorder.<br>• NICE confused "CFS/ME" with other fatigue states and has married together two opposing views : the psychiatric model which says "unhelpful illness beliefs", "thoughts, feelings, behaviours" and "over-vigilance to symptoms" perpetuate the illness, and the biomedical model. This has led to a flawed document that meets no-one's real need, | | |

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| | | • There are proven vested interests in portraying ME as a psychiatric syndrome, as opposed to a seriously debilitating physical illness, with multi system dysfunction, as highlighted by Ian Gibson MP in his Inquiry (2006)<br>• The GDG was selective in the symptoms listed (i.e. emphasising psychosocial symptoms whilst ignoring primary biomedical symptoms)<br>• People with ME/CFS have been shown to be extremely sensitive to pharmacotherapy; this is denied in the Guideline, which is a complete rejection of the patients' experience as well as the scientific evidence.<br>• NICE placed unreasonablemphasis upon the seriously flawed and biased Systematic Review of the literature carried out by the Centre for Reviews and Dissemination (CRD) based at York. [xxx].<br>• The actual number of studies on which NICE relied to support its management recommendations is very small and therefore inadequate for these studies to be used as the "evidence-base" of the safety and efficacy of the regime recommended for implementation nationwide.<br>• NICE recommended that laboratory tests which in other countries have established the organic nature of ME/CFS and which point to potential therapeutic | | |

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| | | interventions should be specifically forbidden in the UK<br>• NICE disregarded the fact that patients are almost universally opposed to CBT and to GET, because survey after survey has shown that GET can be harmful to people with ME.<br>• NICE recommends "CBT and GET "because it believes that "currently these are the interventions for which there is the clearest research evidence of benefit."(1.6.2.4). However, this "research" (seven Random Controlled Trials (RCTs) of CBT and four RCTs of GET) is at best inconclusive and at worse non-existent. When measured objectively, the CBT trials delivered no statistical change. Regarding the graded exercise therapy (GET) trials, only two RCTs had positive results, but after 24 weeks there were no benefits at all.<br>• There is no process in the Guideline to distinguish between when a patient with ME/CFS is extremely ill and when they are no longer so ill and may be able to cope with gentle rehabilitation.<br>• NICE has produced Guidelines for 19 different clinical conditions. Only in the case of the organic disorder ME/CFS is CBT recommended as the primary treatment of choice. | | |
| St | No | We suggest that you await the publication of the PACE trial | | |

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| Bartholomew's Hospital CFS/ME service | | (www.pacetrial.org). | | |
| BRAME (Blue Ribbon for the Awareness of Myalgic Encephalomyelitis) | No | BRAME are disappointed that the decision has been reached that the guidelines on ME do not require a review, as we strongly believe that the current guidelines do not accurately represent the neurological illness Myalgic Encephalomyelitis. This view is held not only by ourselves, patients, and other national and local ME organisations, but also by many healthcare professionals, including experts in ME, and HCP organisations such as the Association of British Neurologists and those representing psychologists/psychotherapists.<br><br>The guidelines must state that ME is a neurological condition as classified by the World Health Organisation (ICD10:G93.3), and recognised as such by the Department of Health. To exclude this classification does not mean that research will be inhibited, but that HCPs continue to be misinformed about the neurological status and severity of this illness, and they treat this condition, and the patients, with little, if any respect. In fact the lack of recognition in the guidelines for the neurological nature of the condition, and the lack of biomedical research in the scope of the document, has, in fact, led to less commissioning of research into the aetiology and pathogenesis of ME. and has led only to more research trying to erroneously prove that CBT and GET do work – despite patient evidence to the contrary<br><br>The current guidelines inhibits accurate diagnosis, and in fact are causing more misdiagnosis, as the guidelines are being misread as including the "NICE Diagnostic Criteria" – this is leading to GPs/HCPs thinking that you can diagnose ME with just fatigue and one other symptom – leading to misdiagnosis and mismanagement. ME is a severe and complex neurological condition that cannot be diagnosed by fatigue + one other symptom, especially given that most people with ME do not cite | It would have been helpful if you had included the original scope in the review document so that people could more easily respond to this question.<br><br>The scope should be adjusted to give greater weight to patient evidence. This is a condition where, in the majority of areas, the only evidence is patient evidence, particularly for the severely affected and children/young people. The evidence that patients give must be given greater weighting in respect of this – particularly as this is supposed to be a patient-led, patient-centred, NHS which encourages the patient expert!<br><br>The aetiology and pathogenesis of neurological ME were excluded from the original scope, which in turn led to the exclusion of the majority of the biomedical research into ME, meaning that we could not even discuss them in the meetings. With more and more research showing sub-grouping, genetic anomalies (including the nervous and immune systems), retroviruses and evidence of on-going infection – the scope must be adjusted to include the | The current guidelines do not give adequate weight to patient evidence and in particular patient evidence relating to the severely/very severely affected and children/young people. By not giving adequate weight to the patient evidence, particularly in these cases, the guidelines are creating an inequality of evidence.<br><br>The current guidelines themselves are creating an increased inequality of care, in particular, biomedical care for people with ME, reinforcing poor health outcomes and QALY. The guidelines are also creating an inequality in research funding, with money mainly going towards trying to prove that the recommendations of the NICE guidelines are correct – CBT and GET, and not biomedical research into the aetiology and pathogenesis of the condition. |

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| | | fatigue as their main symptom. This section was never meant to be a diagnostic criteria, and I repeatedly said that it would be misread and perceived as such, and was repeatedly assured that NICE would put out a statement dispelling this, if it occurred – I brought it to the attention of the NCPCC that the misunderstanding was occurring, and was told that no statement would be put out. This is being further complicated by the NHS Choices website, which is citing in its 'Map of Medicine' feature for HCPs, that they use the "NICE Criteria" for diagnosis. This situation must be rectified immediately, as it is causing a large amount of misdiagnosis and mismanagement, and is also creating a misrepresentation of the serious nature of this complex neurological condition by reducing it to fatigue.<br><br>The guidelines must be rewritten to recommend the use of the Canadian clinical diagnostic criteria – the only clinical diagnostic criteria in the world, which has been found to be, at present, the most accurate in correctly identifying people who have ME. The diagnostic criteria, and accompanying guidelines, were written, as a consensus document, by some of the world's leading doctors and researchers with decades of experience of ME and CFS.<br><br>One of the biggest problems patients face is the continued disbelief of HCPs that ME is a serious neurological condition, and this current guideline with its 'diagnostic criteria' and management recommendations, reinforces HCPs in their erroneous belief that ME is just patients who are "a bit tired" and just need to "believe or exercise themselves well".<br><br>There are also major problems with the list of blood tests. In particular the non-inclusion of ferritin tests for everyone, especially for women who are menstruating, as there are multiple cases of iron deficient anaemia not being picked up till late, leading to long-term iron deficient anaemia, because they have a near normal haemoglobin level but extremely low ferritin levels – Ferritin must be included for everyone. | aetiology and pathogenesis of ME.<br><br>The scope of the research paper review should also be adjusted. The York review had a narrow scope, so in the example of GET it only searched for papers on GET and ME/CFS, it did not however search for papers on Exercise and ME/CFS – if it had extended its parameters it would have found the wealth of papers showing that exercise has an adverse effect on people with ME, and showed potential harm eg cardiovascular and mitochondrial functions. By excluding these papers the document gives a slanted view on the effects of exercise on people with ME. Any further research paper review must also include biomedical papers examining aetiology and pathogenesis, and sub-grouping.<br><br>The guidelines will never be truly revised, until the scope is changed to include biomedical evidence relating to the aetiology and pathogenesis of this serious neurological condition. | |

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| | | The current guidelines also recommend erroneous, and potentially harmful, “treatments”. CBT and GET are shown, in multiple patient surveys, as being harmful/unhelpful for the vast majority of patients. The recommendations are also including people for whom the cited RCTs were never meant to be extrapolated to include, CBT/GET were only found to be helpful to some mild and mild to moderate ambulant adult outpatients – there is no research of effectiveness for moderate, moderate to severe, severe, and very severe patients, nor is there research for the children and young people. CBT/GET, even elements of them, should not be recommended for the severely affected and children/young people, this is potentially extremely dangerous. Not only are CBT and GET not helpful, and potentially harmful, to patients, but they are also at least four times more expensive than the management techniques that patients do find helpful (pacing and symptom control), therefore not giving a good QALY result alongside, poor health outcomes and, potentially, harming the patients.<br><br>The current guidelines consistently ignores the wealth of patient evidence especially for the severely affected and children/young people – the groups for whom there is no evidence apart from patient evidence, and for this to be ignored leads to mismanagement and further harm for patients. The guidelines fail to acknowledge the deaths of people with ME, which are sometimes due to misdiagnosis/mismanagement, but are also due to unrecognised co-morbid conditions. There was also post-mortem evidence presented to the group, which was not acknowledged, showing damage to the central nervous system – proof of biomedical aetiology/pathogenesis.<br><br>The section on the severely affected should be rewritten to more accurately represent the needs of the severely affected. This was the only section in the ‘draft’ consultation that received mostly positive comments, then it was reduced by over two thirds and rewritten, and is now one of the worst sections. | | |

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| | | One of my biggest concerns, when the guidelines were produced, was that the existing biomedical centres for ME would become psycho-social therapy centres, with no follow-up care and monitoring – and this has happened – patients are being diagnosed, given initial 'therapy' (GET/CBT) then leaving, even the most severely affected, abandoned back into the community to the care of GPs who, in most part, neither understand or believe in this serious neurological condition, let alone know how to appropriately manage this complex condition.<br><br>The guidelines must be rewritten – I have even heard from PCT officials who believe, as the majority of the patient population does, that the guidelines are not fit for purpose – but have apologised to patients because they feel that they have to follow NICE guidance. Please help the patient population for one of the most neglected severe neurological conditions in this country, and call for a rewriting of these guidelines, which will take into account biomedical evidence, biomedical HCPs experienced in neurological ME, and patient evidence – to not do so, will only continue the misdiagnosis and mismanagement and a greater inequality of care for patients with a complex and serious neurological condition, who are abandoned without adequate appropriate care.<br><br>BRAME strongly feels that the decision to not hold a review of the NICE guidelines on ME/CFS is wrong. We believe that a review, and rewriting, urgently needs to take place which will take into account biomedical evidence, biomedical HCPs experienced in neurological ME, and patient evidence. Patients cannot wait another three years for the guidelines to come up for review again.<br><br>BRAME are happy to help in any way with the review and rewriting of the guidelines on ME/CFS. On a personal note, I have always been saddened that I was forced by NICE, at the end of the process, into the position where I had to resign from | | |

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| | | the GDG, but have always said that I would be part of any review/rewriting. I hope that you will consider my experience, not only as an expert patient with severe ME, but also as a member of the original GDG on ME/CFS, who has always upheld the confidentiality of the process and the meetings.<br><br>We have also attached, as supportive evidence, our responses to the consultation NICE guidelines, and to the final NICE guidelines, as both are still relevant. | | |
| Invest in ME | No | Response posted separately at the end of the document as too large for the table | | |
| Welsh Association of ME & CFS Support | No | WAMES is disappointed that the feedback NICE has received from its various sources has come to the conclusion that there is not a need for review of CG53. This document has been heavily criticised by patient organisations, patients and respected professional organisations as being prescriptive in its offering of 3 approaches only which do not address any underlying physical abnormalities. There are large patient surveys which show that GET & CBT offer limited effectiveness and can in some cause their condition to worsen (MEA 2010). There are other UK and worldwide patient surveys which show similar results but with smaller patient numbers.<br><br>The Fatigue Intervention by Nurse study found that the intervention was statistically insignificant at 1 year follow up and that supported listening was not an effective treatment for CFS/ME therefore the results were not ineffective as is stated in your review proposal (p.5 Centre for Clinical Practice review) .<br><br>WAMES believes that the term CFS/ME covers a heterogenous group of patients and that the prescriptive nature of the present guidelines does not address the wide variation in patient need and the need for individual management of each patient. | WAMES feels that there is new evidence that could and should result in a review of CG53 at this present time. We list below some of the new studies which show that the interventions of GET and CBT are no longer appropriate interventions for the mild and moderately affected CFS/ME patient group.<br><br>1. Scientists at the University of Dundee found abnormalities in the white cells of children with CFS/ME in 2010.<br><br>2. Knoop et al 2007 found no objective benefit in cognitive function pre/post intervention in their study on CBT.<br><br>3. Twisk & Maes 2010 found that GET and CBT are potentially harmful for many | If the NICE guidelines are to be seen as being thorough then changes need to be made to take account of the advances in published literature on CFS/ME and the need for different approaches to GET & CBT which address the underlying physical problems which have been highlighted in these studies. |

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| | | We feel that research evidence showing biological abnormalities has been published on Pubmed which should have been taken into account when considering any review.<br><br>WAMES is therefore calling on NICE to review Guideline CG53 and to take into account the research evidence that has emerged since this guideline was developed and to also make it more acceptable to patients and the organisations who support them. | patients with CFS/ME.<br><br>4. Wilborg et al 2010 which shows that CBT does not increase physical activity in CFS patients.<br><br>In several studies between 2000 and 2005 of GPs attitudes and knowledge of CFS/ME the following findings were revealed.<br>Bowen et al ME/CFS it has been shown that 28% of UK GPs did not accept that ME/CFS was a recognisable clinical entity (n:105a).<br>Thomas and Smith (2005, p.46) reported that "the level of Specialist knowledge of CFS in primary care remains low. Only half the GP respondents (Wales) believed that the condition actually exists.<br>This shows a need for better education and understanding of this patient group by health professionals and a need for guidelines which show the heterogeneous nature of this patient group.<br><br>We feel the information held in CG53 on Pacing is inaccurate and misleading and is not the same as 'pacing' as practised by patients.<br><br>We must also mention the recent studies on the XMRV virus which, although do not prove causation they do show in some studies that this | |

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| | | | virus is found in CFS patients and therefore testing for this virus should be included in the blood work up.<br><br>We also note that the Department of Health and other devolved nations in the UK have now banned all present and previous patients with a diagnosis of CFS/ME from donating blood. If nothing else this should be included in any guidelines as it shows that the Government is now recognising that ME/CFS should be brought in line with other relapsing/remitting conditions such as MS. | |
| ME-letterforce National e-group | | New information about the NICE Evidence Base for randomised controlled trials of cognitive behavioural therapy and graded exercise therapy used for CG53 suggests that questionable means may have been harnessed to obtain results for these RCTs.<br>I believe there is an urgent requirement for a rigorous independent scientific investigation of these trials and the manner in which they may have been conducted.<br>In particular, a scientific and ethics inquiry should examine the unreliable nature of much self-reporting in these trials, and should also investigate the dangers of inaccurate recall (memory), the problems of what appear to be intense therapist and participant research pressures (to obtain the 'right' results for the investigators and their funders) which operate both consciously and unconsciously, and the issue of what appear to be the exploitation of other peoples good nature (and need), among other more technical matters.<br>Until such action is requested and executed independently (from outside the UK culture), in the interests of public safety, and in light of this new information, I believe that the trials in question | | In the Guideline CG53 it is stated that (p6 Full Version) "A further problem created by the lack of adequate research evidence is the sometimes widely divergent and hotly contested beliefs about CFS/ME".<br>Under such extreme and unique circumstances, which are certainly not the fault of members of the public, I believe it was a discriminatory act against a profoundly disabled minority not to include an equal number of severely affected individuals to serve on the GDG, who could have easily been |

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| | | should now be removed from the literature.<br>The PACE Trial Management Group Manuals describe behaviours and techniques that should not, and I believe, cannot be considered ethical by any independent and reasonable observer.<br>Hence fresh disturbing insight has been provided into previous CBT and GET trials.<br>It is possible that this new information may or may not represent a more or a less sanitised version of the underlying culture of previous if now archaic trials.<br>Much of the written information and instruction to therapists and doctors appears highly exploitative (of other people, their insecurities and knowledge levels, and a relative scientific ignorance of ME).<br>The use of emotional or psychological and group pressure to encourage or convince a member of public to ingest a pharmaceutical product, would be recognised by the reasonable observer as unacceptable and manipulative, not least where the product is of the persuader's own invention.<br>As one example of many similar instances 1) the instruction: “in order to get her to take our drug, it is important that you convey to her a belief in the reality of her symptoms, distress and handicap” would be viewed by most observers as abusive.<br>Similarly 2) Pressurising members of the public into take a drug through the use of misleading analogies (involving other diseases), misleading claims of cure, or other misleading statements, would be seen by the reasonable observer as abusive.<br>Both 1) & 2) and a variety of similar abuses can be found in the PACE Trial Manuals.<br>Instead of drugs, the references are to the non-drug therapies CBT and GET.<br>Sharpe euphemistically points to and downplays the obvious and dangerously intractable problem (a): “Psychological treatments also raise a number of issues about consent and coercion. Although it is often assumed that modern therapy is collaborative, it is important to consider issues of personal | | intelligently facilitated, to match the number of lay GDG members who were not severely affected. Equally, I believe it was a discriminatory act against a minority, under these extreme conditions, not to directly involve publicly respected scientific experts of comparable abilities and experience and numbers, to those who have been engaged in other NICE Guideline GDGs. |

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| | | vulnerability".<br>If people can be led by therapists to remember entire events that never actually happened ((b ) Sharpe & Nutt), then people are placed in considerable danger by opinionated and scientifically untrained therapists, and the results of their RCTs, which ought to be bound by standards higher than those currently accepted for drug RCTs, but which do not even reach that basic standard.<br>"Questions of authority and reality merit further attention" according to Sharpe (a).<br>Given the widely acknowledged human propensity to conform ((c ) Milgram), and the problems posed by therapist actions (often propelled unconsciously) and the unreliability of self reporting, if the difficulties are such that greatly higher RCT standards than drug RCTs are unattainable in this context, then scientific claims must be dropped and a clear statement introduced to that effect. This would ensure that the Human Right (10) to (honest) information is respected, and ordinary members of the general public can swiftly identify and understand any alleged "therapeutic" claims from behavioural RCTs (CBT & GET), which cannot be applied universally, and RCTs (under closer scrutiny) that are little other than manipulative attempts at "cooling out" (some) public anger over the manner in which ME is handled in the UK, but are allowed to masquerade as science, and are eagerly exploited for their blame the victim message, against the public interest, by the insurance industry and the Department of Work and Pensions.<br><br>(a) Sharpe MC Neuroethics workshop report – April 2005 Page 11<br>http://web.archive.org/web/20050520045121/http://www.mrc.ac.uk/pdf-ne uroethics_workshop_2005-2.pdf )<br>(b) Uncritical positive regard? Issues<br>in the efficacy and safety of<br>psychotherapy<br><br>Nutt D J Sharpe M C Journal of Psychopharmacology 22(1) (2008) 3–6) | | |

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| | | http://www.lefnet.hu/resources/userfiles/file/Rihmer/Nutt - Psychotherapy.pdf<br><br>(c)“Obedience to Authority: An Experimental View” Milgram S 1974 Tavistock Publications | | |
| Royal College of Physicians | Yes | The Royal College of Physicians is grateful for the opportunity to comment on the proposed review decision. We would like to make the following points:<br><br>Overall, we would agree that there is no new evidence to suggest that the existing guideline should be amended at present. However, it may need to be reviewed sooner rather than later depending on the outcome of the PACE trial which should give very valuable information about appropriate management in the future. We would recommend that NICE takes this into account when scheduling next review.<br><br>Recently there has been much more interest in CFS/ME from the biomedical research community (including the MRC). However, there have been relatively few good trials in this area.<br><br>It is should be noted that considerable excitement exists regarding the potential role of a retrovirus (XMRV) in the causation of CFS and the potential that may have for antiviral treatment. There is no convincing data for anti virals (and may never be) but in due course an authoritative statement may be required from NICE to discourage the use of unproven approaches. | | |
| The Fatigue Service, Royal Free Hampstead NHS Trust | No | There is no new evidence to suggest a change in assessment or treatment as yet, although there may be soon.<br><br>The PACE Trial results are due out in the near future, and any review should probably happen soon after that; and other | It might be useful to review the list of recommended blood tests; for example, the apparent increase in vitamin d deficiency and insufficiency, and how to interpret | Access to services and treatment for the severely affected still an issue – many have not had a medical assessment for |

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| | | considerations could be taken into account then. | this in the CFS/ME context; ditto, ferritin both as an APR, and in restless leg syndrome. I am sure that others will be suggested as well.<br><br>Many hopes were raised with the initial implications of the XMRV. While it is undoubtedly a contaminant, as the succession of papers has shown, it might be useful to have an outline of why and how medication, such as anti-virals, may not be of value, especially long term, in the treatment of CFS/ME. | years, and sometimes never |
| Royal College of Pathologists | Yes | | The original scope of the guideline and subsequent published guideline did not address the area of aetiology and pathogenesis. Although this is a challenging area, without a review of available evidence rational diagnosis and therapy is difficult and given that existing case definitions are heavily reliant on subjective clinical symptoms and have not been validated against population controls it is critical to review current understanding of aetiology & pathogenesis.<br>There is an extensive literature on potential diagnostic testing in CFS/ME but no clear pattern emerges. Assessing available diagnostic tests for their validity, and performance in appropriate disease and control groups is critical in order | |

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| | | | to underpin clinical diagnosis and develop rational approaches to adjunctive therapies, in addition to ensuring cost-effectiveness for the NHS and for patients themselves.<br>It is recommended therefore that the following areas be included in the scope of any updated guideline:<br>1. Aetiology & pathogenesis<br>2. Clinical utility of diagnostic tests currently available | |

Comments that were too large for the table are pasted below:

| COMMENTS TOO LARGE FOR COMMENTS TABLE | |
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| **Stakeholder Organisation:** | **2 x stakeholder groups – 1) East Anglia ME Patient Partnership (EAME) 2) 25% group**. Listed and counted as 2 separate responses in table above , but as comments are identical the full text is posted once**.** |

**Stakeholder Response to NICE CG53 Three Yearly Review**

**East Anglia ME Patient Partnership (EAME)**

**November 2010**

INTRODUCTION

In accordance with the stakeholder consultation process of 1 to 14 November 2010 concerning NICE's scheduled 3 year clinical guideline review I write with reference to:

1. The National Institute for Health and Clinical Excellence (NICE) Clinical Guideline 53 entitled *'Chronic fatigue syndrome / Myalgic encephalomyelitis (or encephalopathy); diagnosis and management'* published in August 2007.

2. The related *'National Institute for Health and Clinical Excellence Centre for Clinical Practice Review consultation document'* dated 1 November 2010.

I am deeply concerned with Clinical Guideline 53, the flawed process of its production, the failure of NICE to professionally and scientifically review matters and failure to produce a genuine clinically excellent evidence-based guideline for Myalgic Encephalomyelitis (ME) patients in accordance with standards set out in the European Union AGREE Instrument[1].

***[xxx]***

In stark contrast to the case for development of other clinical guidelines, the NICE CG53 Guideline Development Group (GDG) did not contain one disease-specific Hospital Consultant specialist experienced in treating adult patients.

***[xxx]***

Neither in the opinion of many experienced professionals did NICE properly assess all of the international scientific

data on ME/CFS (see below).

***[xxx]***

As NICE Stakeholders, Dr Gibson and his GSRME colleagues were unimpressed with both the composition/expertise of the CG53 GDG and their assessment of the available scientific evidence. An indication of the objective and open-minded approach NICE guideline developers *should have* taken is therefore given in the published report of the GSRME which unequivocally called for what NICE and the GDG failed to do (see below):

> ***"The Group was very interested in the international evidence submitted and concerned as to why this evidence has not been seriously examined in the UK. The Group calls for a further Inquiry into the Scientific Evidence for CFS/ME by the appropriately qualified professionals. This Inquiry should be commissioned by government undertaken by an independent panel of scientific and medical experts, including virologists, immunologists, biochemists etc who can objectively assess the relevance and importance of the international scientific data."***[4]

Please therefore note and act upon the following. Failure to produce a genuine 'clinically excellent' evidence-based guideline for ME patients and their medical practitioners has done much harm and is nothing short of an abuse of taxpayers' money and professional responsibility.

<u>NICE, MEDICAL TAXONOMY & DISCRIMINATION</u>

NICE failed in its mandatory obligation to abide by international disease classification standards and, in unscientific opposition to those standards, conflated physical illness with psychiatric illness.

NICE is procedurally bound to comply with World Health Organisation (WHO) disease classification as set out in the tenth revision of the WHO International Classification of Diseases (ICD 10).

That this is so has been repeatedly confirmed by UK government ministers. In written evidence dated 11 February 2004 for example, Lord Warner, then Parliamentary Under Secretary of State at the Department of Health, confirmed that it is mandatory for UK health agencies to abide by WHO/ICD medical taxonomy.[5]

NICE's own internal documentation, Progress Report Number 8, dated 18 September 2002 from NICE Communications Director Anne Toni Rodgers (a report that was specifically drawn to the attention of NICE's Board) is unequivocal on such matters. In section 2.7.1 entitled *'Institute Classification System'* stating:

> ***"2.7.1.1. Following discussions with Department of Health and other national agencies the Institute has adopted a new classification system that will be applied Institute wide…"***
> ***"2.7.1.4. The ICD-10 classification has been used as the basis for the new Institute classification…"***
> ***2.7.1.5. The World Health organisation (WHO) produces the classification and ICD-10 is the latest***

***version. ICD-10 is used within the acute sector of the NHS and the classification codes are mandatory for use across England."***

*Myalgic Encephalomyelitis/ME* (myalgic = muscle-pain; encephalo = brain; myelitis = spinal-cord; encephalomyelitis = inflammation of brain & spinal-cord) is a serious long-term physical and disabling disease that has been in the medical literature since the 1930s and recognised by the World Health Organisation (WHO) as a physical illness since 1969. The illness disrupts neuro-endocrine-immune function and has long been associated with viral infection[5a]. That such disease classification signifying inflammation of the CNS (brain & spinal cord) is scientifically justified has also recently been attested to by leading internationally respected ME and HIV/AIDS specialist Professor Nancy Klimas:

***"…there is a chronic inflammation, neuro inflammation, and it upsets the whole balance of your systems… the patients become terribly ill…. The immune system is really cranked up; it's a tremendous amount of inflammation. I think that if doctors could get in their heads that it's sort of like lupus or one of these really inflammatory disorders… it is that level of inflammation. There's a tremendous amount of inflammatory stuff going on, and there's a lot of inflammation in the brain itself."***[6]

The WHO categorises *Benign Myalgic Encephalomyelitis (ME)* as a biomedical/neurological disorder in section G93.3 of its tenth/current revision of the *International Classification of Diseases (ICD 10)* where it is also known as *Post Viral Fatigue Syndrome (PVFS)*. The WHO has confirmed that the term *Chronic Fatigue Syndrome (CFS)* is listed only in the ICD-10 tabular index as a "colloquial" reference to ME/PVFS and that ME/PVFS is expressly excluded from mental/behavioural classification[7]. Mental/behavioural *Fatigue Syndromes (FS)* are encoded by the WHO under the separate section F.48 of ICD 10 and should not be conflated with ME/PVFS.

On 23 January 2004 the WHO stated in writing:

***"This is to confirm that according to the taxonomic principles governing the Tenth Revision of the World Health Organisation's International Statistical Classification of Diseases and Related Health Problems (ICD-10) it is not permitted for the same condition to be classified to more than one rubric as this would mean that the individual categories and subcategories were no longer mutually exclusive".***

On 5th February 2009 the WHO stated in writing:

***"I wish to clarify the situation regarding the classification of neurasthenia, fatigue syndrome, post-viral fatigue syndrome and benign myalgic encephalomyelitis. Let me state clearly that the World Health Organisation (WHO) has not changed its position on these disorders since the publication of the International Classification of Diseases, 10th Edition in 1992 and versions of it during later years. Post-viral fatigue syndrome remains under the diseases of nervous system as G93.3. Benign myalgic***

***encephalomyelitis is included within this category. Neurasthenia remains under mental and behavioural disorders as F48.0 and fatigue syndrome is included within this category. However, post-viral fatigue syndrome is explicitly excluded from F48.0".***

The WHO therefore clearly feels it is important to separate physical Central Nervous System/CNS (neurological) illnesses from mental or behavioural disorders and, in using the PVFS label, the WHO implicitly recognises the incidence of viral infection in ME (of which there is a long history[8]).

Invention of the vague term 'Chronic Fatigue Syndrome' in 1988 trivialises the disease that is ME/PVFS. Fatigue of varying degrees is not only present in a virtually all disease, it is a normal and transient by-product of exertion in healthy individuals and is entirely different from serious post-exertional malaise, pain and disability experienced by ME sufferers[9]. It is arguably no more appropriate to call ME/PVFS 'Chronic Fatigue Syndrome' than it would be to describe HIV-AIDS, cancer or leukaemia as such. Lest anyone view such a comparison as trivial I would refer them to recent comments by internationally respected AIDS and ME specialist, Professor Nancy Klimas:

***"I hope you are not saying that [ME/PVFS] patients are not as ill as HIV patients. I split my clinical time between the two illnesses, and I can tell you that if I had to choose between the two illnesses (in 2009) I would rather have HIV"***[10].

'Myalgic Encephalopathy' is not the same clinical entity as Myalgic Encephalomyelitis, it is a more generalised brain disorder or syndrome, of which it is stated in many medical dictionaries:

***"…the hallmark of which is an altered mental state."***

'Myalgic Encephalopathy' is not classified as a specific disease entity by the WHO in ICD 10 at all and is most certainly not permitted as an alternative label for Myalgic Encephalomyelitis or Post Viral fatigue Syndrome that are classified in ICD 10 at section G93.3.

In using the term Myalgic Encephalopathy in the title and construction of CG53 therefore, NICE is abandoning its obligation to adhere to international standards of medical taxonomy. CG53 recommends limiting biomedical investigations that have been shown to reveal serious physical pathology in ME patients (such as impedance cardiography and brain imaging). In recommending such inadequate assessment of patients along with primary clinical reliance upon psychological therapies (CBT/GET) which assume misplaced patient beliefs maintain illness, NICE has disregarded the evidence-base (see below) and has improperly conflated mental and physical illness. Denying patients proper recognition and appropriate treatment in accordance with international standards is a violation of patients human rights and amounts serious discrimination against a vulnerable minority group by NICE.

On these grounds alone, CG53 is "unfit for purpose" and should be rewritten by a new, properly competent and representative Guideline Development Group.

SCOPE OF CLINICAL GUIDELINE 53

The scope/remit of NICE CG53 was/is far too narrow and indicated an improper psycho-social bias even before the Centre for Reviews and Dissemination (CRD) had prepared a summary of the evidence-base and before the GDG had considered such evidence. The scope/remit simply *assumed* behavioural rehabilitative strategies would enhance patients' functional abilities: even though the earlier systematic assessment of the evidence-base for such treatments for the Chief Medical Officer found it seriously wanting[11]. Thus the Welsh Assembly, one of the official commissioning bodies of NICE CG53, stated its purpose was:

> ***"To prepare for the NHS in England and Wales, guidance on the assessment, diagnosis, management of adjustment and coping, symptom management, and use of rehabilitative strategies geared towards optimising function and achieving greater independence for adults and children of (sic) CFS/ME. ...The NICE Guideline is one of three strategies for taking forward improved services for CFS/ME in England. The other two are (a) research, through the MRC Panel; and (b) service development which is now being taken forward by the CFS/ME Service Investment Steering Group.***[12]

The *Medical Research Council (MRC)* research mentioned here was overwhelmingly geared to examining psychosocial interventions in the form of the *PACE Trial* (at a time when biomedical ME research applications to the MRC were regularly dismissed[13]) and the *Service Investment Steering Group* was setting up NHS 'CFS/ME' clinics around the country designed to deliver CBT/GET.

It is unprofessional and unscientific for NICE to have made assumptions in favour of behavioural 'rehabilitative strategies' in advance of assessing the evidence-base. On these grounds alone, CG53 is "unfit for purpose" and should be rewritten by a new, properly competent and representative Guideline Development Group.

INADEQUATE APPRAISAL OF THE EVIDENCE-BASE

In 2006, Harvard Medical School's Professor Anthony Komaroff stated the following at a United States Government CDC (Center for Disease Control) press conference:

> ***"...there are now over 4,000 published studies that show underlying biomedical abnormalities in patients with this illness. It's not an illness that people can simply imagine that they have and it's not a psychological illness. In my view, that debate, which has waged for 20 years, should now be over"*** [14].

Two useful professional overviews of such biomedical evidence, available online, are:

***Myalgic encephalomyelitis: a review with emphasis on key findings in biomedical research***. Professor M Hooper. J Clin Pathol 2007; 60:466–471.
Doi:10.1136/jcp.2006.042408.
http://jcp.bmj.com/cgi/content/abstract/60/5/466

***ME/CFS (WHO ICD-10 G93.3) BIOMEDICAL EVIDENCE SUMMARIES***, Professor Malcolm Hooper, February 2010. Extracts from: *MAGICAL MEDICINE: HOW TO MAKE A DISEASE DISAPPEAR Background to, consideration of, and quotations from the Manuals for the Medical Research Council's PACE Trial of behavioural interventions for Chronic Fatigue Syndrome / Myalgic Encephalomyelitis, together with evidence that such interventions are unlikely to be effective and may even be contra-indicated.* Available online at: www.angliameaction.org.uk/docs/biomedical-evidence-summaries.pdf

In broad terms however, NICE and the appointed Centre for Reviews and Dissemination failed to adequately survey and appraise the evidence-base and presented a wholly inadequate CRD report in 2005 authored by Anne-Marie Bagnall *et al*. Such failure is systematically audited in the January 2006 document by Professor Malcolm Hooper and Horace Reid entitled: ***'Inadequacy of the York (2005) Systematic Review of the CFS/ME Medical Evidence Base. Comment on Section 3 of: The diagnosis, treatment and management of chronic fatigue syndrome (CFS)/(ME) in adults and children, Work to support the NICE Guidelines...'*** The document is available online at: www.meactionuk.org.uk/FINAL_on_NICE_for_Gibson.html

There have long been professional concerns about the selection criteria (particularly the 'Oxford criteria) and quality of research supporting the controversial notion that CBT/GET should be primary treatments for ME/CFS - along with questions surrounding the vested interests of certain individuals advocating use of such interventions to state agencies. This caused the GSRME parliamentary inquiry group to conclude in 2006, with respect to the Oxford criteria and psychosocial advice to Department for Work and Pensions (DWP), for example, that:

> ***"The Group found that the international criteria paid far greater attention to the symptoms of CFS/ME while the Oxford criteria focus very little on any symptoms other than long term tiredness. There is concern that the broad spectrum of patients who may be included in these criteria may lead to inaccurate results in patient studies of CFS/ME. The Group feels that there is room for a further review of the criteria which should be updated, in the light of the peer reviewed and evidence based research done both internationally and in the UK in the last 15 years."***[15]

> ***"There have been numerous cases where advisers to the DWP have also had consultancy roles in medical insurance companies. Particularly the Company UNUM Provident. Given the vested interest private medical insurance companies have in ensuring CFS/ME remain classified as a psychosocial illness there is blatant conflict of interest here. The Group find this to be an area for serious concern and recommends a full investigation of this possibility by the appropriate standards body."***[16]

The cautionary responses of many ME specialists of international repute on CBT/GET have been unequivocal; Dr

Bruce Carruthers, Senior Fellow of the Canadian Royal College and principle lead of the international expert team that produced the highly respected ME Clinical Case Definition states, for example:

> ***"...[Psychiatric lobby] supporters suggest that 'ideally general practitioners should diagnose CFS and refer patients to psychotherapists for CBT without detours to medical specialists as in other functional somatic syndromes'. Proponents ignore the documented pathophysiology of ME/CFS, disregard the reality of patient's symptoms, blame them for their illness and withhold medical treatment. Their studies have often included patients who have chronic fatigue but excluded more severe cases as well as those who have other symptoms that are part of the clinical criteria of ME/CFS."***[17]

It is also notable that the MRC/DWP-funded FINE/PACE Trials into such psychosocial CBT/GET behavioural techniques have run into difficulties. Both use the controversial 'Oxford' patient selection criteria and other means of non-randomly selecting patients and both include leading principle investigators with ties to the medical insurance industry. The FINE Trial has been a failure and the PACE Trial subject to prolonged publication delay. Both are the subject of a serious formal complaint by Professor Malcolm Hooper on alleged grounds of scientific and ethical malpractice. See for example:

> ***Magical Medicine: How to make a Disease Disappear*** and ***Ethical and Scientific Concerns about the MRC PACE Trial***, both by Professor Malcolm Hooper, at:
> www.meactionuk.org.uk/magical-medicine.htm
> www.meactionuk.org.uk/MREC-complaint.htm

The evidence-base upon which the GDG made its CBT/GET primary 'treatment' recommendations was wholly inadequate and is systematically exposed as such by Dr Neil Abbot, senior ME researcher of ME Research UK who states:

> ***"In my professional opinion, no rational reviewing body could have, on this rudimentary evidence base before it, recommend cognitive behaviour therapy (CBT) and graded exercise therapy (GET) as the main treatments for CFS/ME patients. In effect, the RCT evidence base relied upon by NICE to produce Guideline 53 was of poor quality compared with the evidence bases available for other illnesses, and NICE should not have attributed it the usual weight attributed to RCT evidence in the hierarchy of evidence. …It would have been preferable for NICE and the GDG to recognise that specific, rigorous, evidence-based recommendations for treatment cannot be made at present than to incorporate an inadequate evidence-base into established national Guidelines which feed into clinical care and government policy."***[18]

The full text of Dr Abbot's statement is included in **Appendix 1 below** and is also available online at: http://angliameaction.org.uk/NICEJRdocs/Neil_Abbot_MERUK_WS.pdf

The GDG should therefore only have recommended CBT/GET be further examined in a research setting, if at all, and most certainly should not have recommended they be rolled out across the country as primary therapies. The poor quality of CBT/GET RCTs (questionable patient selection criteria, follow-up etc) relied upon by the GDG can only be surpassed by the sheer paucity of studies undertaken on low numbers of patients. This is best-illustrated by comparing the evidence-base for the main NICE-recommended treatments for Multiple Sclerosis (MS) with those for 'CFS/ME'. In 2003 the NICE evidence-base for MS consisted of 80 systematic reviews with over 1100 RCTs examining nearly 90,000 patients. All NICE had to go on for 'CFS/ME' was just 1 systematic review with only 14 RCTs examining less than 1500 patients. A fuller referenced summary of such comparisons is available online at: http://www.angliameaction.org.uk/docs/nice-rcts.pdf

The contrast could hardly be more pronounced and on these grounds alone, CG53 is "unfit for purpose" and should be rewritten by a new, properly competent and representative Guideline Development Group.

CONTRAINDICATIONS TO CG53 & RESEARCH DEVELOPMENTS

One of the most astonishing aspects of CG53 is the failure of the GDG to recommend patients be fully assessed by physical examination using the latest techniques. It is negligent of the GDG to effectively suggest clinicians assume for example that viral infection, immune abnormalities, oxidative stress and inflammation do not play an ongoing key role. This is particularly so when the presence of such pathologies may seriously contraindicate the GDG's recommended of Graded Exercise Therapy (up to and including aerobic level) and there is a long and documented history of such factors in ME/PVFS.

Documented biomedical abnormalities include for example:

> ME/PVFS may include clinical syndromes linked to infectious agents and toxic exposures [19-23 – incl]. Epstein Barr virus, ciguatoxin [21], organophosphates and organochlorines [20, 22].
>
> Immune System, including:
> • chronic immune activation and dysfunction [30, 36-38] evidence of persistent viral infection [39] (enteroviral [42-49], EBV [50-555] and HHV-6/7 [51, 53-58]), activation of the 2-5A anti-viral pathway [55, 59-64], low natural killer cells and cytotoxicity [41, 55, 62, 65-71], T-cell abnormalities [67, 69-70, 72-74], pro-inflammatory cytokines and inflammation [74-80], increased cell apoptosis (death) [81-82] and allergy [62, 83-84].
> • abnormal immuno-genetic expression [69, 74, 86-89].
>
> Brain/Central Nervous System, including:
> • objective measurement of dysfunction [62, 90-94] –deficits in working memory, concentration, information processing [95-103], autonomic function [104-106] (incl. neurally mediated hypotension and orthostatic

intolerance).

• abnormalities –regional brain hypoperfusion [107-114] by SPECT, white and grey matter abnormalities [114-120] by MRI, inflammation [74, 114-115, 121-122], hypomyelination [91, 121-122], neurotransmitter [123-124, 127] and metabolic dysfunction [125-129] by MRS/PET and abnormal spinal fluid proteins [130-131].

• abnormal neuro-genetic expression [122].

Endocrine System: impaired activation of the hypothalamic-pituitary-adrenal (HPA) axis [132-139] and abnormalities of neuroendocrine-genetic expression [86].

Heart and Circulatory System: hypoperfusion [62, 91, 107-114, 140-144], impaired vascular control [35, 142-145] (incl. abnormal response to acetylcholine), low blood volume [142-143], vasculitis [144-145] (incl. raised oxidative stress, inflammation and arterial stiffness [146-147]) and heart dysfunction [140, 143, 148-149].

Muscular: structural and biochemical abnormalities [46, 76, 97, 150-156] including impaired muscle recovery after exercise [157-162] (exercise responsive gene expression abnormal, worsening after exercise [163]).

Others: gastrointestinal dysfunction [164-166] including food intolerance [167-168] and IBS [164, 169], mitochondrial dysfunction [46, 90, 133, 170-171] including abnormal mitochondrial associated gene expression [172] and ion transport channelopathy [163, 173-174].

It is vitally important that a properly competent and representative GDG be set up to reappraise CG53 and the broader evidence-base: particularly given certain recent key peer-reviewed publications. The following is by no means and exhaustive list but is an indicator of documents and studies that should be urgently examined by a reconstituted, representative and competent GDG:

***Statements of Concern about Cognitive Behavioural Therapy and Graded Exercise Therapy provided for the High Court Judicial Review of February 2009.*** M Williams, at: www.meactionuk.org.uk/JR_Statements_-_extracts.htm

***Documented Pathology seen in ME/CFS that contra-indicates the use of Graded Exercise Therapy***. M Williams, at: www.meactionuk.org.uk/Documented_pathology_seen_in_ME-CFS.htm

***Is the Chronic Fatigue Syndrome an Exercise Phobia? A case control study***. W C R Weir *et al*, *Journal of Psychosomatic Research*. Doi: 10.1016/j.psychores.2005.02.002.

***Is Physical Deconditioning a Perpetuating Factor in Chronic Fatigue Syndrome? A controlled study on maximal exercise performance and relations with fatigue, impairment and physical activity***. E Bazelmans *et al*, *Psychological Medicine, 2001, 31, 107-114.*

***ME Patient Exercise – Consequences upon Brain Blood Flow. The Negative Effects of Exercise on an ME/CFS Dysfunctional Brain***. Extracts from *The Clinical and Scientific Basis of ME/CFS* by Byron Hyde MD *et al*. ISBN: 0-969-5662-0-4. Available at: www.nightingale.ca and said extracts available at: www.angliameaction.org.uk/docs/Dr-Byron-Hyde--SPECT-Scans--Post-Exercise--Brain-Blood-Flow.pdf

***Chronic Fatigue syndrome: Harvey and Wessely's (bio)psychosocial model versus a bio(psychosocial) model based on inflammatory and oxidative and nitrosative stress pathways***. M Maes & F N M Twisk. *BMC Medicine 2010, 8:35.* www.biomedcentral.com/1741-7015/8/35

***Biochemical and Vascular Aspects of Pediatric Chronic Fatigue Syndrome.*** Kennedy G, Kahn F, Hill A, Underwood C, Belch J. Archives of Pediatrics & Adolescent Medicine. 2010;164(9):817-823. Doi:10.1001/archpediatrics.2010.157 http://archpedi.ama-assn.org/cgi/content/abstract/164/9/817

***Detection of an Infectious Retrovirus, XMRV, in Blood Cells of Patients with Chronic Fatigue Syndrome.*** Mikovits JA, Dean M, Silverman RH et al. ***Science***. 2009, 326:585-589. www.sciencemag.org/cgi/content/abstract/1179052 www.wpinstitute.org/xmrv/index.html

***Detection of an Infectious Retrovirus, XMRV, in Blood Cells of Patients with Chronic Fatigue Syndrome.*** Lombardi VC, Mikovits JA, *et al*. ***Virulence*** *1:5, 1-5; September/October*. 2010. www.landesbioscience.com/journals/virulence/article/12486

***Detection of MLV-related virus gene sequences in blood of patients with Chronic Fatigue Syndrome and healthy blood donors***. Alter & Komaroff *et al*, PNAS, August 2010. Doi: 10.1073/pnas.1006901107. www.pnas.org/content/early/2010/08/16/1006901107.full.pdf+html

***Biology and pathophysiology of the new human retrovirus XMRV and its association with human disease***. Alice Rusmevichientong *et al*. Immunol Res, 18 August 2010. Doi:10.1007/sI2026-010-8165-y. www.springerlink.com/content/w07qx0236q801q39/fulltext.pdf

Two separate prestigious peer-reviewed journals (Science/PNAS) have now published American studies associating ME/CFS with retroviral infection. Similar results, awaiting publication, have now been found by researchers in several European countries including the UK. As a result of such findings, various countries have now banned ME/CFS patients from donating blood in order to protect national blood supplies. It is interesting to note that, from 1 November 2010, ME patients in the UK are similarly banned for life from donating blood. UK Government officials would however have us believe that this is not to protect the national blood supply from risk of viral infection as in other

countries, but rather to prevent ME patients being made ill by the exertion expended whilst donating blood. This simply beggars belief given that NICE has recommended patients be given graded exercise up to and including aerobic exercise.

There is clear evidence that retroviruses are associated with extremely serious disruption of immune and other bodily function and present in at least some ME patients. There is clear evidence that virus infection inflames bodily tissues and is worsened by exercise in ME patients. There is evidence of raised oxidative stress that is worsened by exercise in ME. There are therefore further and urgent reasons for a properly competent GDG to reassess recommendations in CG53 to limit biomedical assessment of ME patients and recommendations to undertake graded exercise programmes. Under such circumstances it seems scientifically and morally negligent for NICE to dismissively state in its current CG53 Review Consultation Document[175]:

> ***"No evidence was identified that was relevant to research recommendations in the original guideline."***
>
> ***"Conflicting evidence on the association between retrovirus and CFS/ME were also highlighted. However, this is considered outside the remit of the original guideline."***

On these grounds alone, CG53 is "unfit for purpose" and should be rewritten by a new, properly competent and representative Guideline Development Group.

WASTE OF TAXPAYERS' MONEY

Not only was the evidence base for recommending CBT/GET for ME patients wholly inadequate and increasingly GET is found to be contraindicated, it is clear that such misguided "therapies" for ME patients are a gross waste of precious NHS resources and of taxpayers' money. In his witness statement to the High Court, Dr Neil Abbot unequivocally concludes:

> ***"As evidence of efficacy from RCTs is the bedrock of cost-benefit analysis, it also follows from the above that no valid conclusions about the overall cost-effectiveness of CBT and GET for CFS/ME patients can be drawn from the evidence available: such cost effectiveness estimates would be unsound, and could not form the reliable basis on which to allocate funds from the UK Government."***[176]

Moreover, it is not just the cost of providing such therapies one needs to consider. Giving useless or contraindicated therapies to ME patients in place of genuine evidence-based treatment and care can only limit any chance patients have of recovering from the disease. It therefore prolongs and deepens dependency upon state welfare services.

On these grounds alone, CG53 is “unfit for purpose” and should be rewritten by a new, properly competent and representative Guideline Development Group.

CONCLUSION

It is clear that many professionals with a specialist interest in ME have grave concerns about CG53, the competence of the GDG that constructed it and the questionable scope/remit which framed it. A number of them have gone on public record with such concerns: including making statements to the High Court on the matter. Note for example the witness statement comments of Dr Terry Mitchell (one of the longest serving NHS Consultant ME/CFS specialists in the UK), Dr Bruce Carruthers (Lead author of the international specialists’ diagnostic protocols produced in Canada), Professor Malcolm Hooper (Emeritus Professor of Medicinal Chemistry and Scientific Advisor to the 25% ME Group for the Severely Affected) and Dr Ian Gibson (Chairman of the Parliamentary GSRME and NICE Stakeholder):

> ***“Until recently I was for many years the Consultant clinical lead (CNCC) of the Norfolk, Suffolk & Cambridgeshire NHS ME/CFS Service. …I confirm that I was hugely disappointed to find that the membership of the GDG did not include any of my clinical colleagues who over the years have seen large numbers of patients with ME/CFS. In my view this resulted in an unbalanced analysis as many who were on the GDG seemed to have strong leanings to the psychological / psychiatric approach to this devastating illness. ...I also have to say that I was astonished to discover that the systematic evidence review (authored by Bagnall et al – York/CRD 2005), specifically commissioned to support the NICE ME/CFS guideline, omitted the serious concerns highlighted in their previous review of the same literature (JAMA 2001) that such evidence was seriously flawed.”*** (Dr Terry Mitchell [177]).
>
> ***“The NICE document does not aid the clinician by offering guidance about defining symptomatology of ME/CFS as an aid to diagnosis and treatment: all it does is offer a cook-book diagnostic process that must be followed, and then recommends two non-specific behavioural approaches that are not treatment-based… Overall, the process and the resulting Guideline are, in my opinion, detrimental to both patients’ best interest and to best clinical practice. The present Guideline cannot by any standards be considered as providing “best practice advice on care of people with CFS/ME” nor is it “based on the best available evidence” as it claims. In my opinion it should be withdrawn.”*** (Dr Bruce Carruthers[178])
>
> ***“Patients with ME/CFS need practical help and support. Given the inappropriateness of the Guideline, it is inevitable that patients with ME/CFS will continue to receive little or no appropriate healthcare and in the UK, the severely affected will remain invisible, maligned, abused or abandoned. It would be preferable for NICE to recognise that specific, rigorous, evidence-based recommendations for treatment cannot be made at present than to incorporate an inadequate evidence-base into established guidelines”*** (Professor Malcolm Hooper[179])

***"…the guidelines understate the potential harm with graded exercise… That the GDG did not adequately consider the large body of existing international evidence means they were in no position to make the recommendations they did on the use, efficacy and safety of such therapies*** *[CBT/GET]****… the GDG relied upon a very small number of controversial randomised control trials (RCTs). The patient selection criteria for participating in the trials were too wide and therefore allowed non-ME/CFS sufferers to participate… NICE would do better to honestly admit that their core therapy recommendations are not properly evidence-based, and to use this admission as the starting point for an adequately-funded search for a cure. Far too many doctors appear to have lost sight of that objective. …The NICE GDG also failed to endorse the World Health Organisation definition of ME/CFS as a neurological disorder despite the fact that the Department of Health and Government Ministers have repeatedly confirmed that they do agree with this classification. I do not believe that the NICE CFS/ME Guidelines are fit for purpose.*** (Dr Ian Gibson MP[180])

The report of the Parliamentary Group on the Scientific Research into ME (GSRME)[181], a stakeholder in the development of CG53, rightly called for the following measures to be urgently completed in our country:

***CFS/ME. Although some interesting biomedical research has been done in the UK precedence has been given to psychological research and definitions. The Group believes the UK should take this opportunity to lead the way in encouraging biomedical research into potential causes of CFS/ME. There is a great deal of frustration amongst the CFS/ME community that the progress made in the late 1980s and early 1990s toward regarding CFS/ME as a physical illness has been marginalised by the psychological school of thought."*** (Report Page 32).

***"The Research areas defined by the CMO Report in 2002 have not been addressed. Further research is the single most important area in this field."***(Report Page 33).

***"There is a need for diagnostic tests but this is likely to be dependent on a greater understanding of possible causes."***(Report Page 33).

***"There is a need to undertake further research of post viral infective cause in carefully controlled studies."***(Report Page 33).

***"The evidence for a toxin aetiology requires critical and controlled studies. This includes research into possible causes, like pesticides."***(Report Page 33).

***"Much more study should be centred on the reasons why some individuals are susceptible to developing the illness or illnesses. These include further follow-up of immunological, endocrinological and neurological disturbances."***(Report Page 33).

***"The MRC should call for research into this field recognising the need for a wide ranging profile of research. The committee would like to see a similar arrangement to the AIDS programme funded previously by the MRC."***(Report Page 33).

***"An independent scientific committee must examine the wealth of international research data. To exclude it from the debate is a great injustice to patients."***(Report Page 33).

***"We recommend that this condition be recognised as one which requires an approach as important as heart disease or cancer. There is no compelling evidence it is purely psychosocial."***(Report Page 33).

***"This group believes that the MRC should be more open-minded in their evaluation of proposals for biomedical research into CFS/ME and that, in order to overcome the perception of bias in their decisions, they should assign at least an equivalent amount of funding (£11 million) to biomedical research as they have done to psychosocial research. It can no longer be left in a state of flux and these patients or potential patients should expect a resolution of the problems with only an intense research programme can help resolve. It is an illness whose time has certainly come."***(Report Page 34).

It is imperative that NICE support and echo such recommendations. Without such measures being urgently undertaken and without ME being given similar attention and resources as is given to Cancer, HIV/AIDS and other major diseases there can be no genuine 'clinically excellent' treatment recommendations made by NICE.

It is clear that since CG53 was published, there is increasing reason to suppose that the guideline is "unfit for purpose" even within its own over-narrow remit. CG53 should be scrapped, the scope/remit that framed it should be broadened to fully assess disease processes, patient needs and the biomedical evidence-base. A replacement Guideline should be produced by a new, properly competent and representative Guideline Development Group as a matter of urgency.

In conclusion I would like to add endorsement of the stakeholder submission of the national ME charity *Invest in ME*.

Please acknowledge receipt of these stakeholder comments.

East Anglia ME Patient Partnership (EAME).
November 2010.

ENDNOTES

[1] EU AGREE Collaboration / Instrument:
www.agreecollaboration.org/instrument/

[2] July 2008 High Court witness statement for the Judicial Review of NICE CG53 by Dr Ian Gibson - available online at: http://angliameaction.org.uk/NICEJRdocs/Ian_Gibson_WS.pdf

[3] Dr Terry Mitchell, MA MD FRC-Path, Consultant Clinical Lead (CNCC) to one of the 12 national NHS specialist hospital ME/CFS centres - in his witness statement to the UK High Court dated 23 June 2008, available online at:
http://angliameaction.org.uk/NICEJRdocs/Terry_Mitchell_WS.pdf

[4] See page 31 of The Report of the UK *Group on the Scientific Research into ME (GSRME)*, entitled: *Inquiry into the Status of CFS/ME and Research into Causes and Treatment.* November 2006. At the GSRME House of Commons Website:
www.erythos.com/gibsonenquiry/index.html

[5] Cited on page 6 / section 5 of *Corporate Collusion* by Professor Malcolm Hooper, Eileen Marshall and Margaret Williams, September 2007. Available online at:
www.meactionuk.org.uk/Corporate_Collusion_2.pdf

[5a] See:
***Myalgic encephalomyelitis: a review with emphasis on key findings in biomedical research***. Professor M Hooper. J Clin Pathol 2007; 60:466–471. Doi: 10.1136/jcp.2006.042408.
http://jcp.bmj.com/cgi/content/abstract/60/5/466

***ME/CFS (WHO ICD-10 G93.3) BIOMEDICAL EVIDENCE SUMMARIES***, Professor Malcolm Hooper, February 2010. Extracts from: *MAGICAL MEDICINE: HOW TO MAKE A DISEASE DISAPPEAR Background to, consideration of, and quotations from the Manuals for the Medical Research Council's PACE Trial of behavioural interventions for Chronic Fatigue Syndrome / Myalgic Encephalomyelitis, together with evidence that such interventions are unlikely to be effective and may even be contra-indicated.* Available online at:
www.angliameaction.org.uk/docs/biomedical-evidence-summaries.pdf

[6] Professor Nancy Klimas, University of Miami, Department of Neuroendocrine Immune Disorders, in a Miami Radio interview at 11pm on September 19th 2010. See:
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www.pandoranet.info

[7] ***"ME is classified at G93.3 and is a specific disorder. The term CFS, covers many different conditions, which may or may not include ME. The use of the term CFS in the ICD index is merely colloquial and does not necessarily refer to ME. It could be referring to any syndrome of chronic fatigue, not to ME at all. The index (i.e. Volume ii) cannot be taken as definitive."*** [Dr Robert Jakob, Medical Officer (ICD), Classifications,

Terminologies and Standards, WHO H/Q, Geneva, 4th February 2009].

For accuracy, full reference needs to be made to the three-volume published/book version of WHO ICD 10 (especially the alphabetical index/volume 3 as well as the tabular list/volume 1) the bibliographic details of which are:

- *International Statistical Classification of Diseases and Related Health Problems - Tenth Revision – Second Edition: Volume 1 – Tabular List* – ISNB: 92 4 154649 2.
- *International Statistical Classification of Diseases and Related Health Problems - Tenth Revision – Second Edition: Volume 2 – Instruction Manual* – ISNB: 92 4 154653 0.
- *International Statistical Classification of Diseases and Related Health Problems - Tenth Revision – Second Edition: Volume 3 – Alphabetical Index* – ISBN: 92 4 154654 9.

For further background see *ME/CFS: Classification Issues*, by Margaret Williams, 3 May 2009 at:
www.meactionuk.org.uk/ME_CFS_Clasification_Issues.pdf

And note that the three WHO volumes of ICD-10 can be accessed via academic libraries and some public libraries and are of course available directly from the WHO at:
http://www.who.int/classifications/icd/en

[8] See:
***Myalgic encephalomyelitis: a review with emphasis on key findings in biomedical research***. Professor M Hooper. J Clin Pathol 2007; 60:466–471. Doi: 10.1136/jcp.2006.042408.
http://jcp.bmj.com/cgi/content/abstract/60/5/466

***ME/CFS (WHO ICD-10 G93.3) BIOMEDICAL EVIDENCE SUMMARIES***, Professor Malcolm Hooper, February 2010. Extracts from: *MAGICAL MEDICINE: HOW TO MAKE A DISEASE DISAPPEAR Background to, consideration of, and quotations from the Manuals for the Medical Research Council's PACE Trial of behavioural interventions for Chronic Fatigue Syndrome / Myalgic Encephalomyelitis, together with evidence that such interventions are unlikely to be effective and may even be contra-indicated.* Available online at:
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[10] Nancy Klimas, one of the world's foremost AIDS and ME physicians; Professor of Medicine and Immunology, University of Miami; New York Times, 15th October 2009.

[11] *Interventions for the Treatment and Management of Chronic Fatigue syndrome: A Systematic Review*, Penny Whiting, Anne-Marie Bagnall, Amanda J Sowden *et al.* JAMA. 2001;286(11):1360-1368 (doi:10.1001/jama.286.11.1360)
http://jama.ama-assn.org/cgi/content/full/286/11/1360

*The Effectiveness of Interventions used in the Treatment/Management of Chronic Fatigue Syndrome and/or Myalgic Encephalomyelitis in Adults and Children,* The University of York, Report 22, NHS Centre for Reviews and Dissemination, 2002; Anne-Marie Bagnall, Penny Whiting, Kath Wright, Amanda J Sowden. www.york.ac.uk/inst/crd/CRD_Reports/crdreport22.pdf

[12] Welsh Assembly Government Disclosure Log 2296. Full details as to why the Welsh Assembly Government formally requested (Feb 2004) the National Institute for Clinical Excellence to prepare a clinical and service guideline for Chronic Fatigue Syndrome / Myalgic Encephalomyelitis:
http://wales.gov.uk/publications/accessinfo/disclosurelogs/premay10disclosures/dl2200to2299/disclog2296/?lang=en

[13] Dr Jonathan Kerr, for example, of St Georges Hospital was a world-leading researcher into genetic expression and subtyping in ME patients (see below paper) yet his applications at the MRC for biomedical research project grants were repeatedly turned down. In spite of receiving high points from biomedical medical professionals on MRC grants Dr Kerr was effectively vetoed each time by psychiatrists on the panel. See the following as an example of Dr Kerr's seminal biomedical ME/CFS research:
***Seven Genomic Subtypes of Chronic Fatigue Syndrome / Myalgic Encephalomyelitis (CFS/ME): a detailed analysis of gene networks and clinical phenotypes.*** Jonathan Kerr *et al.* Journal of Clinical Pathology. 5 Dec 2007. Doi: 10.1136/jcp.2007.053553.
http://jcp.bmj.com/cgi/content/abstract/jcp.2007.053553v1

[14] Professor Anthony Komaroff, Harvard Medical School: Speaking at the USA Government CDC (Centers for Disease Control and Prevention) press conference on 3 November 2006:
http://www.cdc.gov/media/transcripts/t061103.htm

[15] See page 12 of The Report of the UK ***Group on the Scientific Research into ME (GSRME)***, entitled: ***Inquiry into the Status of CFS/ME and Research into Causes and Treatment.*** November 2006. At the GSRME House of Commons Website:
www.erythos.com/gibsonenquiry/index.html

[16] Parliamentary ***Group on the Scientific Research into ME (GSRME)*** Report, Page 30, November 2006: www.erythos.com/gibsonenquiry/index.html
Also see:
***CORPORATE COLLUSION***. Professor Malcolm Hooper, Eileen Marshall & Margaret Williams:
www.meactionuk.org.uk/Corporate_Collusion_2.htm
For concerns and professional complaints about the Medical Research Council (MRC) and Department of Work & Pensions (DWP) funded PACE Trial (PACE is the acronym for Pacing Activity and Cognitive behavioural therapy, a randomised Evaluation…) on 'Chronic Fatigue Syndrome' see: ***Magical Medicine: How to make a Disease Disappear*** and ***Ethical and Scientific Concerns about the MRC PACE Trial***, both by Professor Malcolm Hooper, at:
www.meactionuk.org.uk/magical-medicine.htm

www.meactionuk.org.uk/MREC-complaint.htm

And see: ***The Mental Health Movement: Persecution of Patients? A Consideration of the Role of Professor Simon Wessely and Other Members of the "Wessely School" in the Perception of Myalgic Encephalomyelitis (ME) in the UK. Background Briefing for the House of Commons Select Health Committee***. Professor Malcolm Hooper. At:

www.meactionuk.org.uk/SELECT_CTTEE_FINAL_VERSION.htm

And see: ***Proof Positive? Evidence of the deliberate creation via social constructionism of "psychosocial" illness by cult indoctrination of State agencies, and the impact of this on social and welfare policy***. Eileen Marshall, Margaret Williams 30th August 2005. At:

www.meactionuk.org.uk/PROOF_POSITIVE.htm

And see: ***Concerns About Commercial Conflict of Interest Underlying the DWP Handbook Entry on ME/CFS. Hooper, Marshall & Williams***.

www.meactionuk.org.uk/HOOPER_CONCERNS_ABOUT_A_COMMERCIAL_CONFLICT_OF_INTEREST.htm

And see: ***Wessely, Woodstock and Warfare?*** Margaret Williams. 9th August 2007. At:

www.meactionuk.org.uk/Wessely_Woodstock_and_Warfare.htm

[17] **Dr Bruce Carruthers**, Senior Fellow of the Canadian Royal College and principle lead of the international expert team that produced the highly respected ME Clinical Case Definition, in: ***Myalgic Encephalomyelitis / Chronic Fatigue Syndrome: A Clinical Case Definition and Guidelines for Medical Practitioners - An Overview of the Canadian Consensus Document*** by Professor Bruce M Carruthers and Dr Marjorie I Van de Sande. UK – NHS Clinician Endorsed / UK A4 Format – Version]:

http://data.eastanglia.me.uk/pdfs/Canadian_ME_Overview_A4.pdf

http://angliameaction.org.uk/docs/CanadianOverviewUK.pdf

[18] See the High Court witness statements of Dr Neil Abbot-

http://angliameaction.org.uk/NICEJRdocs/Neil_Abbot_MERUK_WS.pdf

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APPENDIX 1 – STATEMENT BY DR NEIL ABBOT

**Witness Statement of Dr Neil C Abbot**

**[Fraser & Short v NICE – CO/10408/07]**

**31st October 2008**

I, Dr Neil Abbot, Operations Director of ME Research UK, The Gateway, North Methven Street, Perth, PH1 5PP will say as follows:

1. I make this statement in support of the Claimants' application for judicial review. In particular, I make this statement to address the evidence base upon which the Guideline Development Group relied in recommending Cognitive Behavioural Therapy ("CBT") and Graded Exercise Therapy ("GET") in NICE Guideline 53. Insofar as the facts within this statement are within my direct knowledge they are true. Insofar as they are not, they are true to the best of my knowledge.

**Expertise**

2. I have an MSc in Biomedical Science (1987); PhD in Clinical Physiology (1992); MSc in Medical Statistics (2001), and I have held post-doctoral appointments at the Universities of Dundee, Glasgow and Exeter. To date, I have co-authored some 35 MEDLINE listed scientific papers and articles, including 2 full papers and 2 academic letters on ME/CFS, and am author of a review listed in the Cochrane Database Systematic Reviews. Since 2001, I have been Operations Director of ME Research UK, a national charity which has the primary aim of commissioning and funding biomedical research into ME/CFS, and I currently hold an Honorary Research Fellowship at the Department of Medicine, University of Dundee.

3. The Cochrane Collaboration (an international group founded in 1993 that was developed in response to Archie Cochrane's call for up-to-date, systematic reviews of all relevant random controlled trials of healthcare, the results of which are published in the Cochrane Library) defines a Randomised Controlled Trial (RCT) as: *"An experiment in which two or more interventions, possibly including a control intervention or no intervention, are compared by being randomly allocated to participants"*. An RCT should involve concurrent enrolment and follow-up of the test-

and control-treated groups. The RCT is considered the “gold standard” design for medical research studies, and ideally all medical interventions and clinical practice would be based on RCT evidence: however, the Cochrane Collaboration estimates that at present only "10% to 35% of medical care is based on RCTs".

4. RCTs, however, are only as good as their design, their execution, and what is possible within a particular field of study, and in most fields of enquiry the quality of many RCTs fall far short of the “gold” implied by the term “gold standard”. In particular, they should be adequately “powered” (i.e. have an adequate number of patients in each treatment arm) and have a comparison group as “indistinguishable” as possible from the “treatment” intervention. This latter point is crucial as there is a well-recognised tendency for improvements to be reported by patients taking part in clinical trials, improvements seen in both the “treatment” and comparison groups. If the comparison group is less than comparable, for example when 12 active sessions of a psychological therapy are compared with 12 weeks of inactive “waiting list” waiting, then it is impossible to say whether the reported improvement is due to the “treatment” or due to the events involved in taking part in the trial. Another key issue is outcomes, and RCTs should be measuring meaningful and clinically useful outcome measures: the ideal outcome measures are those considered “hardest”, e.g., death, clinical events such as heart attack, and return to work which is a clearly defined measurable result. In many trials, however, outcomes may be “softer” and/or relate to improvements that might be important to a researcher but less important to the patient in the clinic or in the home.

5. If evidence is from one or two smallish RCTs with comparison groups imperfectly matched to treatment groups (such as when patients undergoing an “active” intervention like CBT are compared with patients “inactively waiting” on a waiting list), the results are considered “suggestive” of a true treatment effect, but nevertheless inconclusive overall, and a clear estimate of a treatment’s true effect over a comparison group can only be gauged by a systematic review, preferably a meta-analysis, involving a substantial number of RCTs conducted in a field. This is the reason for the “Hierarchy of evidence” table, which puts systematic reviews and meta-analysis at the top.

**RCTs Relied Upon in Development of NICE CG53**

6. In the following points, I shall refer to the two reports which informed the deliberations of the Guideline Development Group for NICE Guideline 53:
   6.1) the “York Report” by Bagnall et al. (2005) which comprised NICE Guideline Appendix 1; and
   6.2) the Update to “the York Report” by Bagnall et al. (2007).

7. I shall also refer to the two more recently published (2008) assessments of the clinical trial evidence for some psychological therapies in CFS/ME:
   7.1) A meta-analysis of CBT for CFS (Malouff et al. 2008); and
   7.2) A Cochrane Collaboration review of CBT for CFS in adults (Price et al. 2008)

   Although not before the GDG, both of these studies make similar points about the limitations and heterogeneity of the evidence-base which are of course just as valid now as they were at the time the GDG were considering the

evidence base.

8. The NICE Guideline 53 correctly identifies that the therapeutic interventions which have most supportive RCT evidence in the field of CFS/ME are cognitive behavioural therapy (CBT) and graded exercise therapy (GET), and that there is a paucity of clinical trials in the field of CFS/ME generally.

**CBT**

*Number of RCTs*

9. As regards CBT, the Appendix to NICE Guideline 53 (Section 6.3.3) states that it had identified 10 RCTs which met the inclusion criteria for assessment of CBT. In fact, 4 of these (3 in adults and one in children) were controlled clinical trials, all with very low validity scores, and I shall not discuss the evidential value of these since - low validity scores apart - the limitations of what can be concluded from this design are well-recognised. Therefore, in reality 6 RCTs of CBT proper for CFS/ME were available for assessment, 5 in adults and 1 in children, a fact confirmed by Bagnall et al. (2007) in their update to the York review.

10. Exhibit NCA 1 to this statement is a table giving details of each of the 5 RCTs of CBT in adults, and the single RCT in children.

11. The first thing to note about Exhibit NCA 1 is that 2 of 5 the RCTs in adults have a negative overall result for CBT (Whitehead 2002 when CBT was compared with a "no intervention" control; and Lloyd 1993 when CBT was compared with a placebo injection). The remaining 3 trials have overall positive effects, and moreover have high "validity scores" indicating that they are likely to have been well-designed and conducted. Nevertheless, it is clear that the gold standard evidence-base relied upon by the Guideline Development Group of NICE Guideline 53 for the recommendation of CBT for CFS/ME consists of three mildly positive RCTs only.

12. A useful comparator is the RCT evidence base considered in development of NICE Clinical Guideline 8, November 2003, on Multiple Sclerosis, which consisted of many hundreds of RCTs and many thousands of patients.

*"Power" of RCTs*

13. Furthermore, the RCTs in NCA 1 have relatively small numbers of patients. In 4 of the trials, analysis was performed on ≤30 patients in the CBT groups, while the largest trial (Prins et al. 2001) analysed 92 patients in the CBT arm. Since only 2 of the trials (Deale et al. 1997 and Prins et al. 2001) reported making a power calculation to determine the adequacy of sample size to determine a treatment effect, it is entirely possible that samples in most of this small group of trials were too small to determine a true effect.

14. Again, a useful comparator is the RCT evidence base considered in development of NICE CG 8 on Multiple

Sclerosis.

*Inconsistency of approach in RCTs*

15. Importantly, in this group of RCTs overall, there is a difference between trials in the type and content of CBT delivered, as well as in the number, frequency and length of intervention sessions given. This makes it impossible to say that like was being compared with like as far as type and delivery of "treatment" was concerned. To understand the importance of this, if the treatment was radiotherapy instead of CBT what conclusions would we draw from 5 individual trials (2 of which were essentially negative) if each was examining different forms of radiotherapy at different doses for different durations of time? We should rightly ask that further trials be undertaken with standardisation of radiotherapy type, dose and duration to determine whether or not a true treatment effect really existed.

16. It is also important to note that case definitions differ between trials, raising the question of whether homogeneous groups of patients are being compared between trials. Two of the positive trials recruited patients using the Oxford criteria (1991) which focuses on unexplained chronic fatigue and does not require additional symptoms, whereas the NICE Guideline 53 (section 1.2.1.2) recommends that patients be diagnosed with fatigue characterised by post-exertional malaise and other symptoms such as cognitive difficulties, sleep disturbance, and chronic pain. It might therefore be that those patients diagnosed with CFS/ME according to NICE Guideline 53 make up a different - most probably more sick - clinical group in comparison with the group on which much of the RCT evidence for the use of CBT was derived.

17. Again, NCA 1 shows that each trial has used a different comparison group (placebo injection; relaxation; standard medical care; guided support/natural course; and no intervention) making it impossible to say that the CBT delivered is having a "specific" treatment effect. To establish that, CBT would need to be compared with a comparison "treatment" which gives equal time and an equal quality of care to the patient without using the main elements of the CBT encounter. Until that is done, it remains entirely feasible that good supportive clinical care combined with self-help strategies might be as effective as formal CBT.

*Inconsistency of Outcomes in RCTs*

18. As regards outcomes measured, an array of different outcome measures were used in these 5 RCTs. These include the fatigue subscale of the CIS in Prins et al. 2001; the daily functioning Karnofsky score in Sharpe 1996; the SF-36 physical functioning subscales in Deale 1997; the London Handicap Scale and the CIS in Whitehead 2001; and 10-item visual analogue scales and Karnofsky performance scoring in Lloyd 1993. It is generally agreed that standardisation of outcome measures between trials is the optimum way of assessing and comparing overall effects in systematic reviews and meta-analyses, and that lack of standardisation is therefore a serious drawback to making conclusions.

*Absence of Adequate Follow Up*

19. In 4 of the 5 trials, follow-up was relatively short, and so the relevance of the findings over the medium to long term remains unknown. This is important in an illness like CFS/ME which is a long-term condition, and which has a tendency to chronicity with serious debility in some; a moderate treatment effect in the short-term might not show longer term gains. As an example of this, the one trial (Deale 1997) in which 5-year follow-up results were reported revealed no significant difference between the CBT and the control group as regards physical functioning and fatigue after 5 years, though quality of life was reported to be improved.

*Children*

20. As regards children with CFS/ME, only a single RCT of CBT in children (Stulemeijer 2005 in Table 1) was available for consideration by the Guideline Development Group of NICE Guideline 53. As it is impossible to draw a conclusion about treatment provision nationally from a single RCT (and impossible to extrapolate from the adult evidence-base to children, particularly for psychological strategies given the differences between the adult and the child mind), no further comment is necessary.

**Why the GDG could not on the evidence base properly have reached its conclusions as to CBT**

21. A review of CBT for CFS/ME was published very recently by the Cochrane Collaboration (Price et al. 2008). A thorough review of the literature by these authors found 15 studies (including controlled clinical trials and some unpublished data, as well as the smaller number of RCTs). It is worth noting its central "Authors conclusions" as they echo the points made above:

    *"…The evidence base at follow-up is limited to a small group of studies with inconsistent findings. There is a lack of evidence on the comparative effectiveness of CBT alone or in combination with other treatments, and further studies are required to inform the development of effective treatment programmes for people with CFS…Whilst the review provides some very preliminary findings for the effectiveness of CBT using an individual modality and using increased activity, further study of these aspects of the CBT interventions are required in order to be able to draw valid conclusions on their superior benefit*"

22. The authors of the 2008 Cochrane review have taken the only measured and realistic view of the clinical trial evidence for the use of CBT in CFS/ME, namely, that a moderate effect of CBT can be measured in some, but not the majority, of patients. It remains unknown, however, whether this overall positive effect of CBT is a "specific effect" since it could well be that good supportive clinical care combined with self-help strategies might be as effective and less costly for the UK tax-payer, as other documents such as the Canadian Consensus Document on ME/CFS (Carruthers et al. 2003) have already suggested. This point is corroborated by the conclusions of another review (Malouff et al. 2008) of the evidence-base for CBT in CFS/ME which stated:

    *"… one can conclude that CBT for chronic fatigue disorders has about the same* [mild to moderate] *efficacy as diverse psychological treatments for a variety of psychological disorders*".

**GET**

23. I now consider the evidence for the recommendation by the Guideline Development Group of NICE Guideline 53 of graded exercise therapy (GET) for CFS/ME. The Appendix to the Guideline (Section 6.3.3) states that it had identified 5 RCT which meet the inclusion criteria for assessment of GET, and with this I concur.

*Number of RCTs*

24. NCA 2 comprises a table giving details of each of the 5 RCTs of GET, all of them in adults.

25. The first thing to note is that 1 of the 5 RCTs had a negative overall result for GET (Wearden 1998) compared with an inactive "diary review " control group, while the remaining 4 trials have overall positive effects, and moreover have high "validity scores" indicating that they are likely to have been well-designed and conducted. Nevertheless, it is clear that the gold standard evidence-base relied upon by the Guideline Development Group of NICE Guideline 53 for the recommendation of GET for CFS/ME relies on four positive RCTs only.

*Power, Inconsistency, Follow-up etc*

26. The points I make about the limitations of what we can conclude from this very small group of RCTs are very similar to the points made above for trials of CBT, so I shall only briefly list my reservations:

    26.1) The RCTs in NCA 2 have relatively small numbers of patients, and the two largest trials split the total number of patients into 4 groups, reducing statistical power.

    26.2) In this group of RCTs overall, the trials differ in the type and content of GET delivered, as well as in the number, frequency and length of intervention sessions given. This makes it impossible to say that like was being compared with like as far type and delivery of "treatment" was concerned.

    26.3) Outcome measured ranged from SF-36 physical functioning subscales in Powell 2001, to the clinical global impression change score in Fulcher 1997 and Moss-Morris 2005, to an array of physiological measures in Wallman 2005, and the Chalder fatigue scale in Wearden 1998. The lack of standardisation of outcome measures is therefore a complication in the interpretation of results.

    26.4) Again, follow-up was relatively short, and so the relevance of the findings over the medium to long term remains unknown.

    26.5) Case definitions differed between trials, three using the broader Oxford criteria and two the standard CDC-1994 raising the question of whether homogeneous groups of patients are being compared between trials.

26.6) Importantly, comparison groups differed between trials, making it impossible to identify the precise treatment effect.

*Drop Outs & Adverse Effects*

27. An important issue raised by this group of RCTs on GET, concerns drop-outs from the study. In the Wearden 1998 study, significantly more drop-outs were observed in the exercise group (25/68, 37%) compared with the non-exercise group (15/69, 22%). Again, Powell 2001 stated that " Twenty one (14%) of the 148 patients who entered the trial dropped out…Of these, 19 were in the intervention groups". There is, therefore, some indication that GET might not be acceptable to a subgroup of patients with CFS/ME, and this should be explored further.

28. The adverse event rate was not reported in any of the 5 trials, a serious omission given the well-documented association of CFS/ME with exercise-related relapse.

**Why the GDG could not on the evidence base properly have reached its conclusions as to GET**

29. Looking at the RCTs of GET overall, the striking thing is the modesty of the scale of their results. Although 4/5 can be classed as "positive" trials in favour of GET, the p-values for the comparison in NCA 2 are generally just inside the level of significance (e.g. $p<0.05$ instead of $<0.001$ or below). The authors of the trials acknowledge this, and some explicitly state what these modest results mean in real patient numbers. For example, Fulcher 1997 state that "Analysis by intention to treat showed that 17 of 33 patients improved with exercise and nine of 33 improved with flexibility treatment…($p=0.04$)", a comment which illustrates both the small numbers in the trial, and the modesty of the findings since a large number of patients reported no improvement. Moss-Morris 2005 reported a similar modest differential between treatment and control groups, while Wallman 2004 stated that there was no significant difference between the two groups in terms of percentage of subjects rating themselves as being better (29/32, 91%) in the GET group compared with 22/29 (76%) a relaxation group.

**Conclusions**

30. Overall, the RCT evidence for CBT and GET identified and considered by the Guideline Development Group of the NICE Clinical Guideline 53 is comprised of 10 trials (5 for each "treatment"). Given that 3 of these RCTs are "negative" evidentially, the conclusions that can be drawn from this extremely small evidence-base are tentative indeed. Particularly worrying is the fact that the group of 10 RCTs exhibits small sample sizes at the group level, and great heterogeneity in terms of outcome measures used, comparison groups studied, and case definitions used to recruit patients. At best, the conclusions about efficacy one could draw from this small group of trials are suggestive and tentative only.

31. As evidence of efficacy from RCTs is the bedrock of cost-benefit analysis, it also follows from the above that no valid conclusions about the overall cost-effectiveness of CBT and GET for CFS/ME patients can be drawn from

the evidence available: such cost effectiveness estimates would be unsound, and could not form the reliable basis on which to allocate funds from the UK Government.

32. In my professional opinion, no rational decision making body could have, on this rudimentary evidence base before it, recommended cognitive behavioural therapy (CBT) and graded exercise therapy (GET) as the main treatments for CFS/ME patients. In effect, the RCT evidence base relied upon by NICE to produce Guideline 53 was of poor quality compared with the evidence bases available for other illnesses, and NICE should not have attributed it the usual weight attributed to RCT evidence in the hierarchy of evidence. The conclusion of the Cochrane Review in respect of CBT (which can be applied with equal if not more force to the evidence base for GET) is the only proper conclusion that can be drawn: *"further study of these aspects of CBT interventions are required in order to be able to draw valid conclusions on their superior benefit."*

33. The practical consequences of NICE's impermissible conclusions can be seen in the "Quick reference guide" to NICE Guideline 53, which is the only part of the extensive guideline read by most healthcare professionals and GPs. On page 6, the Pathway to Care ends at a category called "Specialist CFS/ME care", inside which cognitive behavioural therapy (CBT) and/or graded exercise therapy (GET) are the only "treatments" alongside activity management. Whatever the merits of these therapies in themselves for psychological illnesses, it is irrational for them to constitute the end points of a Pathway to Care. More thorough and detailed research is required before any such striking recommendations can properly be made.

**Statement of Truth**

I believe that the facts in this statement are correct.
Dr Neil Abbot
Dated 31st October 2008.

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**Exhibits/Tables**

[NCA 1] *Table 1. Summary of CBT RCT results (extracted from NICE Full Guideline, Appendix 1, Table 8, page 94; and the updated Bagnall et al 2007)*

| **Principal author and year** | **Case definition** | **Treatment** | **patients (n) total** | **Comparison group** | **Outcomes and effect** | **Duration** | **Overall effect** | **Validity score (Maximum 20)** |
|---|---|---|---|---|---|---|---|---|
| **Adults** | | | | | | | | |
| Lloyd 1993 | Australian | CBT (+ DLE injection) | 90 | Placebo injection only | PH: **NS**; PS: **NS**; QOL: (**p<0.05**) | 1x 60 min session; and 5 x 30-60 min sessions over 12 weeks | <> | 13 |
| Deale 1997, 2001 | Oxford | CBT | 60 | "Relaxation" | PH: (**p<0.01**); PS: **NS**; QOL: (**p<0.05**) | 13 x 60 min sessions over 24 weeks | + | 18 |
| Sharpe 1996 | Oxford | CBT | 60 | Standard medical care | PH: (**p<0.05**); PS: (**p<0.05**); QOL: (**p<0.001**) | 16 x 60 min sessions over 16 weeks | + | 15 |
| Prins 2001 | CDC 1994 | CBT | 270 | "guided support" and "natural course" | PH: (**p<0.01**); PS: (**p<0.01**); QOL: (**p<0.05**) | 16 x 60 min sessions over 8 months | + | 16 |
| Whitehead 2002 | CDC 1994 | CBT by GP | 65 | "no intervention" control | PH: **NS**; PS: **NS**; QOL: **NS** | weekly or every two weeks for 12 months | <> | 3 |
| **Children** | | | | | | | | |
| Stulemeijer 2005 | CDC 1994 | CBT | 69 | Waiting list | PH: (**p=0.03**); School attend (**p=0.04**) | 10 sessions over five months. | + | 16 |

+ indicates a positive effect of treatment; − indicates a negative effect of treatment; <> indicates no effect of treatment
Outcome codes: PH = physical; PS = psychological; QOL = quality of life and general health. Outcomes which showed a significant difference between intervention and control groups are highlighted in bold (NS=not significantly different).

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[NCA 2} *Table 2. Summary of GET RCT study results (extracted from NICE Full Guideline, Appendix 1, Table 8, page 94; and the updated Bagnall et al 2007)*

| **Principal author and year** | **Case definition** | **Treatment** | **patients (n) total** | **Comparison group** | **Outcomes investigated** | **Duration** | **Overall effect** | **Validity score (Maximum 20)** |
|---|---|---|---|---|---|---|---|---|
| Wearden 1998 | Oxford | GET & Fluoxetine | 136 (4 groups) | review of activity diaries/placebo capsule | PH: **NS (0.07)**; PS: **NS**; QOL: **NS** | preferred aerobic activity (usually walking/jogging, swimming or cycling), for 20 minutes, at least three times per week.for 26 weeks | <> | 17 |
| Fulcher 1997 | Oxford | GET | 66 | Flexibility exercises and relaxation therapy | PH: (**p<0.05**); PS: (**NS**); QOL: (**p=0.04**) | Graded aerobic exercise for 12 weeks of trial | + | 17 |
| Powell 2001, 2004 | Oxford | GET | 148 (4 groups) | standardised medical care | PH: (**p<0.001**); PS: (**p<0.05**); QOL: (**p<0.001**) | two individual treatment sessions and telephone follow up, then self-managed graded exercise; 52-week follow-up | + | 17 |
| Moss Morris 2005 | CDC 1994 | GET | 49 | Standard medical care | PH: (**p<0.03)** | Graded exercise for ideal of 30 minutes for 5 | + | 9 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | days per week for 12 weeks | | |
| Wallman 2004 | CDC 1994 | GET | 61 | relaxation/flexibility therapy | PH: (**p<0.027**; PS: (**p<0.027)** | aerobic activity that used the major large muscles, with pacing for 12 weeks | + | 9 |

+ indicates a positive effect of treatment; − indicates a negative effect of treatment; <> indicates no effect of treatment
Outcome codes: PH = physical; PS = psychological; QOL = quality of life and general health. Outcomes which showed a significant difference between intervention and control groups are highlighted in bold (NS=not significantly different).

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Wallman KE, et al. Randomised controlled trial of graded exercise in chronic fatigue syndrome. Med J Aust 2004;180:444-8. , et al.
[NOTE: This statement by Dr Neil Abbot, Operations Director of ME Research UK, The Gateway, North Methven Street, Perth, PH1 5PP, is available in full online at:

http://angliameaction.org.uk/NICEJRdocs/Neil_Abbot_MERUK_WS.pdf

**If there are any areas excluded from the original scope that you feel need to be addressed in any update decision, please write these in the box below**

SCOPE OF CLINICAL GUIDELINE 53

The scope/remit of NICE CG53 was/is far too narrow and indicated an improper psycho-social bias even before the Centre for Reviews and Dissemination (CRD) had prepared a summary of the evidence-base and before the GDG had considered such evidence. The scope/remit simply *assumed* behavioural rehabilitative strategies would enhance patients' functional abilities: even though the earlier systematic assessment of the evidence-base for such treatments for the Chief Medical Officer found it seriously wanting[11]. Thus the Welsh Assembly, one of the official commissioning bodies of NICE CG53, stated its purpose was:

> ***"To prepare for the NHS in England and Wales, guidance on the assessment, diagnosis, management of adjustment and coping, symptom management, and use of rehabilitative strategies geared towards optimising function and achieving greater independence for adults and children of (sic) CFS/ME.***

***...The NICE Guideline is one of three strategies for taking forward improved services for CFS/ME in England. The other two are (a) research, through the MRC Panel; and (b) service development which is now being taken forward by the CFS/ME Service Investment Steering Group.***[12]

The *Medical Research Council (MRC)* research mentioned here was overwhelmingly geared to examining psychosocial interventions in the form of the *PACE Trial* (at a time when biomedical ME research applications to the MRC were regularly dismissed[13]) and the *Service Investment Steering Group* was setting up NHS 'CFS/ME' clinics around the country designed to deliver CBT/GET.

It is unprofessional and unscientific for NICE to have made assumptions in favour of behavioural 'rehabilitative strategies' in advance of assessing the evidence-base. On these grounds alone, CG53 is "unfit for purpose" and should be rewritten by a new, properly competent and representative Guideline Development Group.

**If there are any equality issues relevant to the guideline that you do not feel have been adequately addressed please write these in the box below**

NICE, MEDICAL TAXONOMY & DISCRIMINATION

NICE failed in its mandatory obligation to abide by international disease classification standards and, in unscientific opposition to those standards, conflated physical illness with psychiatric illness.

NICE is procedurally bound to comply with World Health Organisation (WHO) disease classification as set out in the tenth revision of the WHO International Classification of Diseases (ICD 10).

That this is so has been repeatedly confirmed by UK government ministers. In written evidence dated 11 February 2004 for example, Lord Warner, then Parliamentary Under Secretary of State at the Department of Health, confirmed that it is mandatory for UK health agencies to abide by WHO/ICD medical taxonomy.[5]

NICE's own internal documentation, Progress Report Number 8, dated 18 September 2002 from NICE Communications Director Anne Toni Rodgers (a report that was specifically drawn to the attention of NICE's Board) is unequivocal on such matters. In section 2.7.1 entitled *'Institute Classification System'* stating:

***"2.7.1.1. Following discussions with Department of Health and other national agencies the Institute has adopted a new classification system that will be applied Institute wide…"***
***"2.7.1.4. The ICD-10 classification has been used as the basis for the new Institute classification…"***
***2.7.1.5. The World Health organisation (WHO) produces the classification and ICD-10 is the latest version. ICD-10 is used within the acute sector of the NHS and the classification codes are mandatory for use across England."***

*Myalgic Encephalomyelitis/ME* (myalgic = muscle-pain; encephalo = brain; myelitis = spinal-cord; encephalomyelitis = inflammation of brain & spinal-cord) is a serious long-term physical and disabling disease that has been in the medical literature since the 1930s and recognised by the World Health Organisation (WHO) as a physical illness since 1969. The illness disrupts neuro-endocrine-immune function and has long been associated with viral infection[5a]. That such disease classification signifying inflammation of the CNS (brain & spinal cord) is scientifically justified has also recently been attested to by leading internationally respected ME and HIV/AIDS specialist Professor Nancy Klimas:

> ***"…there is a chronic inflammation, neuro inflammation, and it upsets the whole balance of your systems… the patients become terribly ill…. The immune system is really cranked up; it's a tremendous amount of inflammation. I think that if doctors could get in their heads that it's sort of like lupus or one of these really inflammatory disorders… it is that level of inflammation. There's a tremendous amount of inflammatory stuff going on, and there's a lot of inflammation in the brain itself."***[6]

The WHO categorises *Benign Myalgic Encephalomyelitis (ME)* as a biomedical/neurological disorder in section G93.3 of its tenth/current revision of the *International Classification of Diseases (ICD 10)* where it is also known as *Post Viral Fatigue Syndrome (PVFS)*. The WHO has confirmed that the term *Chronic Fatigue Syndrome (CFS)* is listed only in the ICD-10 tabular index as a "colloquial" reference to ME/PVFS and that ME/PVFS is expressly excluded from mental/behavioural classification[7]. Mental/behavioural *Fatigue Syndromes (FS)* are encoded by the WHO under the separate section F.48 of ICD 10 and should not be conflated with ME/PVFS.

On 23 January 2004 the WHO stated in writing:

> ***"This is to confirm that according to the taxonomic principles governing the Tenth Revision of the World Health Organisation's International Statistical Classification of Diseases and Related Health Problems (ICD-10) it is not permitted for the same condition to be classified to more than one rubric as this would mean that the individual categories and subcategories were no longer mutually exclusive".***

On 5th February 2009 the WHO stated in writing:

> ***"I wish to clarify the situation regarding the classification of neurasthenia, fatigue syndrome, post-viral fatigue syndrome and benign myalgic encephalomyelitis. Let me state clearly that the World Health Organisation (WHO) has not changed its position on these disorders since the publication of the International Classification of Diseases, 10th Edition in 1992 and versions of it during later years. Post-viral fatigue syndrome remains under the diseases of nervous system as G93.3. Benign myalgic encephalomyelitis is included within this category. Neurasthenia remains under mental and behavioural disorders as F48.0 and fatigue syndrome is included within this category. However,***

***post-viral fatigue syndrome is explicitly excluded from F48.0".***

The WHO therefore clearly feels it is important to separate physical Central Nervous System/CNS (neurological) illnesses from mental or behavioural disorders and, in using the PVFS label, the WHO implicitly recognises the incidence of viral infection in ME (of which there is a long history[8]).

Invention of the vague term 'Chronic Fatigue Syndrome' in 1988 trivialises the disease that is ME/PVFS. Fatigue of varying degrees is not only present in a virtually all disease, it is a normal and transient by-product of exertion in healthy individuals and is entirely different from serious post-exertional malaise, pain and disability experienced by ME sufferers[9]. It is arguably no more appropriate to call ME/PVFS 'Chronic Fatigue Syndrome' than it would be to describe HIV-AIDS, cancer or leukaemia as such. Lest anyone view such a comparison as trivial I would refer them to recent comments by internationally respected AIDS and ME specialist, Professor Nancy Klimas:

> ***"I hope you are not saying that [ME/PVFS] patients are not as ill as HIV patients. I split my clinical time between the two illnesses, and I can tell you that if I had to choose between the two illnesses (in 2009) I would rather have HIV"***[10].

'Myalgic Encephalopathy' is not the same clinical entity as Myalgic Encephalomyelitis, it is a more generalised brain disorder or syndrome, of which it is stated in many medical dictionaries:

> ***"…the hallmark of which is an altered mental state."***

'Myalgic Encephalopathy' is not classified as a specific disease entity by the WHO in ICD 10 at all and is most certainly not permitted as an alternative label for Myalgic Encephalomyelitis or Post Viral fatigue Syndrome that are classified in ICD 10 at section G93.3.

In using the term Myalgic Encephalopathy in the title and construction of CG53 therefore, NICE is abandoning its obligation to adhere to international standards of medical taxonomy. CG53 recommends limiting biomedical investigations that have been shown to reveal serious physical pathology in ME patients (such as impedance cardiography and brain imaging). In recommending such inadequate assessment of patients along with primary clinical reliance upon psychological therapies (CBT/GET) which assume misplaced patient beliefs maintain illness, NICE has disregarded the evidence-base (see below) and has improperly conflated mental and physical illness. Denying patients proper recognition and appropriate treatment in accordance with international standards is a violation of patients human rights and amounts serious discrimination against a vulnerable minority group by NICE.

On these grounds alone, CG53 is "unfit for purpose" and should be rewritten by a new, properly competent and representative Guideline Development Group.

| Stakeholder Organisation: | Invest in ME |
|---|---|

Invest in ME Response

**BOX 1 – AGREE WITH NICE REVIEW**
**If no, please add any reasons/comments in the box below**

**Background**

Invest in ME (IiME) is a UK charity created by people with Myalgic Encephalomyelitis (ME) or parents of children with ME. The work performed by the charity is voluntary and we are independent and do not have any ties to NHS or government departments which could influence our opinions when analysing these guidelines and we have not accepted government finance in order to support the past government and the NICE guidelines.

Although not an original stakeholder (IiME only became a charity in May 2006) or a member of the GDG the charity nevertheless registered to become a stakeholder for these guidelines and supplied responses to NICE for both the draft guidelines and those published by NICE in 2007.

Invest in ME examined the Full version of the NICE guidelines and also looked at the other documents produced by NICE in all the categories (for patients, carers and the public).

Our response was given to NICE and published on our web site here –
http://www.investinme.org/IIME%20Campaigning-NICE-Guidelines%20IiME%20Response.htm#IiME_Response
From the outset we need to state that Invest in ME and our supporters wish to be a proactive participant in enabling proper science and correct education about ME to be performed. Since Invest in ME became a charity we have devoted a considerable amount of time, effort and money to promote better education.
At the same time we are an independent charity and will not sit on the fence or remain silent when poor decisions are being made about the welfare of people with ME and their families and carers, especially when these decisions are so heavily influenced by vested interests who have so maligned people with ME over the last generation and who continue to weald such unrepresentative influence on establishment policies. Our objective lies not in retaining a status or obtaining an income but to make progress in treating this disease.

We declare here that we have no faith in NICE or that NICE will in any way change their recommendation not to review their NICE guidelines. NICE consultation processes are known to be a farce.
But we comment on this review process so that our comments can go on record and add to the weight of evidence which will eventually force NICE to be reviewed and the conduct and performance of their management to be held to account.

The document received from NICE Centre for Clinical Practice (Review of consultation document) is typical of the scant regard which NICE seems to display for the welfare of people with ME and their families.
NICE took over two years to formulate the Draft Guidelines, which became the published guidelines. IiME, along with those responding to the guidelines, were limited to two months to respond with comments to the Draft Guidelines and received no advance warning of the final contents of the NICE guidelines released in August 2007.

Likewise stakeholders have been given only two weeks to comment on the Review Consultation Practice.

NICE were out of touch with the needs of chronically ill patient needs in 2007 and that distance from reality and awareness continues today.

The Review consultation document provides three clinical areas for discussion. It is these clinical areas, decided by NICE and their GDG, upon which stakeholders are supposed to comment regarding whether the guidelines need to be revised.

In order to comment on the recommendation by NICE not to perform a review of the guidelines it is not sufficient merely to look for new evidence which has come about in recent years - one necessarily needs to look back on the original guidelines to understand what a failing they were and what they missed. We use the comments from our original submission in this document.

There was almost universal condemnation of the guidelines by patients, patient support groups, most ME charities and even healthcare providers. The only organisations who agreed with the guidelines were those who had accepted government money in the past to support government policies on ME or those who had vested interests and gained from promoting ME as a behavioural illness.

The document provides sparse information on the discussions behind this document or on the processes in which a decision was made not to recommend an update to the guideline. No information is forthcoming about who has supplied comments from the original GDG. Transparency seems still not to be a strong point with NICE.

**TAXONOMY USED BY NICE**

Firstly the name of the disease. As we noted in our response to the NICE guidelines the terminology may be crucial in dealing with ME, especially as GPs, paediatricians, other healthcare personnel and the media use different terms.
Let us be unequivocal - chronic fatigue is a symptom, not a disease or illness.

Dr. B. Saraceno of the WHO clarified the classification in writing on October 16, 2001.
"I wish to clarify the situation regarding the classification of neurasthenia, fatigue syndrome, post-viral fatigue syndrome and benign myalgic encephalomyelitis. Let me state clearly that the World Health Organisation (WHO) has not changed its position on these disorders since the publication of the International Classification of Diseases, 10th Edition in 1992 and version of it during later years." "Post-viral fatigue syndrome remains under the diseases of nervous system as G93.3. Benign **myalgic encephalomyelitis** is included within this category."

Benign myalgic encephalomyelitis (ME) and post viral fatigue syndrome (PVFS) are classified under WHO classification ICD 10 G93.3 and chronic fatigue syndrome (CFS) is listed in the tabular index. We would prefer to use the term ME for the illness but also recognise that ME/CFS is used widely. The original NICE standards on terminology were extremely poor and unprofessional and this continues in this review document.
NICE perpetuate the terminological mess around ME.

The name is myalgic encephalomyelitis – not encephalopathy.
The UK government supports this definition of ME as a neurological illness and therefore subscribes and endorses the name of myalgic encephalomyelitis. Myalgic encephalomyelitis must be used by NICE to describe ME.
To do differently is negligent of NICE.

The Consideration of the evidence (chapter 2) in the consultation review document states that 'From initial intelligence gathering and a high-level randomised control trial (RCT) search clinical areas were identified to inform the development of clinical questions for focused searches'

Yet, as Professor Simon Wessely has stated: "*It should be kept in mind that evidence from randomised trials bears no guarantee for treatment success in routine practice. In fact, many CFS patients, in specialised treatment centres and the wider world, do not benefit from these interventions*" [**1**]

**GDG Composition**

The GDG contained no biological expertise and so was invalid to begin with. This was negligent of NICE and the UK government to allow this. To repeat this negligence is something which needs to be challenged. NICE cannot expect to have any of their work endorsed if it fails to adhere to basics of guideline development.
The membership of the Guideline Development Group appeared to have very little expertise in the clinical definition, analysis and research of neurological ME as defined by WHO ICD-10 G93.3. If there are specific levels of expertise, then these should be included but none of the nationally or internationally recognised bio-medical experts in ME are included.

**NICE CLINICAL AREAS**

The Review Consultation Document states 'Three clinical questions were developed based on the clinical areas above, qualitative feedback from other NICE departments and the views expressed by the Guideline Development Group, for more focused literature searches.'
We believe that this should have been opened to all the stakeholders to discuss with adequate time. The GDG was found to be inadequate in producing the original guidelines – how would it be sufficient to allow the same group to be instrumental in deciding whether a review of the guidelines should be proposed and which areas were to be determined to make that judgement?
Certainly those other stakeholders who contributed to reviewing the draft guidelines should have been consulted at the same time as the GDG.

**Clinical Area 1: Case Definitions of CFS/ME**

What are the existing case definitions for chronic fatigue syndrome in adults and children and what evidence exists to substantiate or validate these case definitions?

It is stated that 'No conclusive evidence was identified that would invalidate current guideline recommendations.'

This seems to be very difficult to believe.
One of the main complaints against the original NICE guidelines was that they were too broad and non-specific. This allows misdiagnosis to occur and wrong treatments to be administered. The research by Professor Leonard Jason [**2**] has addressed this issue. Although this Review Consultation document states that it has reviewed this research we cannot understand how this research can be dismissed or not considered as proving that a review of the NICE guidelines is required.
This research by Professor Jason was produced following the Invest in ME International ME Conference 2010 which showed extensive information on the pathology of the illness.
As Professor Jason stated in the conference abstract
"When diagnostic categories lack reliability and accuracy, the quality of treatment and clinical research can be significantly compromised. A misdiagnosis may lead to improper treatment and in cases of severe illness, the matter of an incorrect diagnosis can have serious consequences. In other words, the validity (i.e., usefulness) of a diagnostic category is inherently limited by its reliability." See Journal abstract
The problem lies in the lack of separation of ME from the various fatigue states which NICE seem happy to live with under one definition.

The number of varying diagnostic guidelines is a problem that the ME community has been criticising for a long time. There are at least ten definitions of Chronic Fatigue Syndrome.
In the NICE guidelines and the so-called supporting evidence base a frequently used case definition is the Oxford Criteria which includes patients with no physical signs and selects subgroups of

patients with high levels of psychiatric diagnoses.
This remains too broad a view of fatigue states and underlines the heart of the problem with the way this illness is treated and perceived as it includes far too broad a range of illnesses.

IiME feels that the use of the Oxford criteria for any discussion/diagnosis or treatment for ME invalidates everything and its usage should be terminated forthwith.
The Oxford criteria for "CFS/ME" have no predictive validity and have not been adopted anywhere but in the UK.

Even NICE stated that the Canadian guidelines are more detailed than the Oxford.

The guidelines are a quite biased and narrow-looking report which mixes up far too many illnesses and research information simply to prove the original intention of the document – to force people with ME to be given psychological therapies and repeat the myths of the past.

It also attempts to subjugate ME into a bag of common illnesses all falling under the term CFS. In this NICE have done a major disservice to people with ME who are needlessly suffering from the perceptions of biased healthcare professionals who maintain their views with little good scientific evidence.

This questions the impartiality of NICE and the Guidelines.

The Gibson Inquiry (2006) reviewed diagnostic criteria and concluded that the Canadian criteria were a useful contribution to defining the clinical condition of CFS/ME and were more detailed than the Oxford criteria, for example.

This is central to the whole issue of diagnosis. The Canadian guidelines differentiate between those who have neurological ME and those who have a collection of symptoms which will be classified as idiopathic chronic fatigue.

Correct diagnosis allows each group to be treated accordingly.

IiME concluded that the basis of the NICE Guidelines was in viewing as broad a section of fatigue states as possible, where high quality biomedical research into ME has been ignored. Essential research showing the multi-system nature of ME was ignored and was not considered or discussed, e.g. enteroviruses, orthostatic intolerance and oxidative stress.

There was little in the guidelines that would persuade a GP to conduct a proper and full medical examination before diagnosis.
This is a major failing.

We believe that the paediatric guidelines for ME by Professor Jason et al. warrant a review of this area by NICE [**3**].

**Clinical area 2: Information and support needs**

This posed the question - What are the support needs of healthcare professionals, patients and carers? And concluded no new evidence was identified which would change the direction of current guideline recommendations.

As stated earlier it is not only new evidence which needs to be used to judge whether a review of the NICE guidelines is necessary. With the original guidelines so fundamentally flawed then the needs of healthcare professionals, patients and carers are already compromised. One has to look at

the guidelines to highlight what was at fault.

**Co-Morbidities**

Healthcare providers need to be aware of the co-morbidities with ME and the way that the disease can progress. The guideline does not address the management of co-morbidities. These are as important as the illness

NICE state that "*At present, there are no physical signs that identify CFS/ME specifically*". The Canadian Guidelines are helpful in making a diagnosis as a collection of symptoms need to be present and the hallmark symptom of post excertional malaise needs to be present before a diagnosis can be made.

With no review of the biomedical research available then NICE have been negligent in not providing any information on co-morbidities with ME.

Jason et al (2006) reported that the mean age of patients with myalgic encephalomyelitis/chronic fatigue syndrome dying from heart failure, i.e. 58.7 years, is significantly lower than the age of those dying from heart failure in the general US population, i.e. 83.1 years. These findings implicate that ME/CFS is a risk factor to cardio-vascular disorder." [**4**]

Healthcare professionals and patients/carers need to be aware of possible treatments and be educated in what not to do. With the NICE guidelines providing criminally negligent advice to use GET for ME patients then lack of proper awareness of the disease progression can be fatal.

**Recovery**

Healthcare professionals and patients and carers need to have knowledge of recovery rates.

NICE stated that "*Most people with CFS/ME will improve over time and some people will recover and be able to resume work and normal activities.*"

There is no credible evidence of this and there is a lack of large scale epidemiological studies that address the question of recovery.

Bell and Bell did a study on the definition of recovery in Chronic Fatigue Syndrome and found that all persons in that study had persistent symptoms on several questionnaires despite claiming to be 'recovered or 'nearly recovered'. [**6]**

The guidelines stated that the majority of individuals with mild CFS/ME will still be working. Where is the evidence for this?

No epidemiological studies can substantiate this.

Studies by ME Research UK show that around 50% are employed but struggling to maintain their lives, with another 40% existing on benefits.

This was a different spin on the facts.

Most "*mildly affected*" will not "*use the weekend to cope with the rest of the week*". This is so generic as to be unusable. Many students for example will use the weekend to make up for lost time during the week.

The guidelines give a false view to healthcare professionals with unsubstantiated claims and therefore a review is not only advisable but it is a necessity.

**Depression**

NICE stated that "Higher depression scores were noted among CFS/ME patients in some studies but it was unclear whether depression occurred before or after CFS/ME symptoms began."

How would this compare to other chronic illnesses?

This is a skewed spin which NICE use to denigrate ME patients.

Again the guidelines provided an incorrect picture of the illness and the negligence shown by NICE and the GDG increases.

**NICE Bias**

The psychological approach was comprehensively retained from the draft guidelines and these guidelines failed to address this with a balanced approach by excluding the compelling biomedical research that shows the organic nature of ME and which will likely dictate the diagnosis and treatment of ME.

**Judicial Review**

Clinical Area 2 states that in terms of information and support needs of CFS/ME patients, carers and healthcare professionals, most identified studies focused on educational interventions to improve knowledge of CFS/ME among healthcare professionals. No new evidence was identified which would change the direction of current guideline recommendations

In the original guidelines Preface Professor Richard Baker stated that
"*The publication of this guideline presents an opportunity to improve care for people with CFS/ME*. "

That was a very true statement. However, we noted that it was a sad failing of NICE that these guidelines failed to grasp this opportunity and instead delivered a weak and ineffectual document that seemingly attempted to retain much of the ignorance and prejudice existing within healthcare provision for ME. The guidelines provided little to further the treatment of ME and NICE chose only to use the evidence which satisfied a predetermined view that CBT and GET are preferred methods of treatment for ME, that there is doubt about the true nature of ME and that CFS incorporates ME within its catchment.

It is no small matter that the very population for whom the NICE guidelines were supposedly intended to benefit were instead forced to take NICE to a Judicial Review, such was the dissatisfaction with the guidelines.
Over twenty internationally renowned ME/CFS experts provided Statements in support of the Claimants' case for the Judicial Review of the National Institute for Health and Clinical Excellence (NICE) Clinical Guideline on "CFS/ME" that was brought by ME/CFS sufferers [**5**]

The comments by these experts are damning and show the complete dissatisfaction with the NICE guidelines and they are repeated here as additional reasons why the NICE guidelines need to be reviewed –

**Malcolm Hooper, Professor Emeritus of Medicinal Chemistry**
**University of Sunderland**
**November 2007**
"In my view, the Guideline is biased and over rigid in its recommendations and will put a large number of ME sufferers at risk of harm through its strong recommendations for the use of CBT and GET.

CBT is based on the idea that somatoform disorders are maintained by abnormal or unhelpful illness beliefs which lead to abnormal or unhelpful behaviour. The first requirement for a somatoform diagnosis is that there is no physical cause for the symptoms. This is not the case in ME/CFS"

**Dr William Weir, Consultant Physician**
**November 2007**
"Two forms of treatment…are CBT and GET. CBT is a psychological treatment. Its application in what is certainly an organic disorder is basically irrational. Its putative mode of action is based on the proposition that patients with ME/CFS feel unwell because they have an 'abnormal illness belief', and that this can be changed with CBT.

It has never been proven to be helpful in the majority of patients with ME/CFS. GET comprises a

regime of graded exercise, increasing incrementally over time.

It has been almost universally condemned by most patient groups.

A number of patient surveys have shown it to be, at best, unhelpful, and at worst, very damaging.

Its application is counter-intuitive, particularly when one of the most debilitating and well recognised symptoms of ME/CFS is post-exertional malaise which can put some patients in bed for days after relatively trivial exertion"

**Dr Terry Mitchell,**
**formerly Consultant Clinical Lead (CNCC)**
**Norfolk, Suffolk & Cambridgeshire NHS ME/CFS Service**
**23rd June 2008**
"The GDG has placed undue reliance upon a small number of RCTs that were methodologically flawed because they did not adequately define the patient population"

**Dr Jonathan Kerr**
**Hon. Consultant in Microbiology**
**Consultant Senior Lecturer in Inflammation**
**Principal Investigator of the CFS Group**
**St George's University of London**
**11th August 2008**
**"**The predominance of psychologists / psychiatrists on the Guideline Development Group is entirely inappropriate and has led to a biased analysis in my opinion. The GDG has placed undue emphasis on a few UK clinical trials which support the use of psychological treatments; however, these studies did not properly or adequately define their patient population"

**Dr Irving Spurr**
**Newcastle ME Research Group**
**12th August 2008**
"…..I consider that the recommendation of CBT and GET as blanket treatments of 'clinically excellent' first choice is extremely dangerous to patients.

I am concerned that NICE claims that an adequate evidence base supports CBT/GET, when in fact the Guideline Development Group (GDG) relied almost exclusively on a handful of extremely controversial RCTs (random controlled trials). I have no doubt that patients in the research quoted by the GDG did not have ME/CFS"

**Dr Eleanor Stein**
**Psychiatrist**
**Alberta, Canada**
**12th August 2008**
"My overall impression reading the (NICE) Guidelines for the first time was one of alarm.
I will limit my comments to the deficiency which has the greatest potential for harm to patients.
The NICE Guidelines do not make any reference to the biomedical literature on ME/CFS.
A physician who is new to the field and who has not had time to read the thousands of paper reporting measurable abnormalities in ME/CFS may get the impression that:

(1) Biomedical issues are irrelevant in ME/CFS and that
(2) CBT and GET actually make the core symptoms of people with ME/CFS better.
A close read of the literature reveals that none of the core symptoms of ME/CFS improve with CBT or GET. The recommendation for GET stems from the often quoted but unproven assumption that deconditioning causes or exacerbates ME/CFS.
In fact this assumption has been disproven (Bazelmans et al 2001; Harvey et al 2008) and cannot therefore be used as a basis for treatment.

Informed consent is an ethical requisite in the practice of medicine.
Informed consent requires that patients embarking on any therapy be told the potential benefits and risks of the therapy being recommended.
Meeting this legal standard in ME/CFS requires that patients be told about the potential benefits and risks of CBT/GET.
If patients are being coerced to believe what is not true, psychological trauma can result.
If patients are pushed to increase activity beyond their capabilities, exacerbation of symptoms can be expected. The NICE Guidelines are biased towards a particular model of CBT/GET that is widely viewed as ineffective and potentially unethical"

**Dr Byron Hyde, Clinician specialising in ME**
**having examined over 3,000 patients between 1984 – 2008**
**Ottawa, Canada**
**15th August 2008**
"(Graded exercise therapy) is not therapy – it is simply the enforcement of an opinion rather than a treatment based upon any scientific examination of a patient's pathology and treatment of that pathology.

I believe that those who developed (the) graded exercise programme as a valid treatment of ME have already been soundly criticised to the Courts. I also believe scientific evidence that such a programme is against the best interests of ME patients has already been presented. The benefit of such a programme is to the interests of the insurance industry and not the patient. Graded exercise programmes may be significantly dangerous to many of these ME patients"

**Dr Derek Enlander**
**Virologist specialising in ME/CFS**
**formerly Assistant Professor at Columbia University**
**and Associate Director of Nuclear Medicine at New York University**
**Physician-in-Waiting to the UK Royal Family**
**and to members of HM Government when they visit New York**
**18th August 2008**
"(The GDG) produced a Guideline that recommends CBT and GET as the prime treatment yet there is in fact published evidence of contra-indication / potential harm with GET. This has been published by independent researchers (e.g. Peckerman et al).

The NICE GDG claims that CBT/GET is supported by significant research. In fact the GDG relied almost exclusively on specious reports which are unproven"

**Dr Nigel Speight**
**Consultant Paediatrician specialising in ME/CFS**

**20th August 2008**
"I regard the continuing aura of disbelief surrounding the illness and mainly emanating from the psychiatrists as detrimental to both medical progress and the interests of sufferers"

**Dr Terry Daymond, Consultant Rheumatologist**
**and recently Clinical Champion for ME for North-East England**
**22nd August 2008**
"It is with regret that I note that the NICE Guidelines do not take into account recent developments in the management of ME. They lean towards a psychological and psychiatric basis, when it is now recognised that there are a large number of medical problems associated with ME.

Recent studies on genetics, the central nervous system, muscle function and persistent infections have shown that there is a great deal of medical information available with regard to the management of ME"

**Dr Bruce Carruthers**
**Consultant Physician**
**Vancouver, Canada**
**29th August 2008**
"Research from the 'organic school' identified many pathophysiological abnormalities in patients with ME/CFS resulting from dysfunction in a number of vital control systems of the body such as the central nervous system, the autonomic nervous system, the endocrinological system and the immune system.

The attitude of the 'psycho-social' school continues to be to largely ignore this research. It seems they can only maintain their hypothesis by discouraging the search for an organic basis and by denying the published evidence, which they are certainly doing.

This unseemly battle of ideas has been settled politically by proclamation and manipulation, not by science, and not by fair and open means. CBT and GET appear to be based on the rationale that patients with CFS/ME have 'faulty' belief systems concerning the 'dangers' of activity, and that these aberrant beliefs are significant perpetuating factors.

If CBT to 'correct' these 'false' beliefs can be combined with a graded exercise programme to re-condition these patients, it is virtually promised that a significant proportion of them will improve both their attitude and their physical functioning, and thus cure their illness. Using CBT, patients are therefore to be challenged regarding their 'aberrant' thoughts and expectations of relapse that the 'psycho-social school' psychiatrists believe affect symptom improvement and outcomes. Cognitions concerning fatigue-related conditions are to be addressed; these include any alleged 'over-vigilance to symptoms' and reassurance-seeking behaviours, and are to be dealt with using re-focusing and distraction techniques.

It is when a therapy such as CBT begins to interfere with the natural warning systems, of which both pain and fatigue are a part, that the increased risks arise. In particular, musculo-skeletal pain and fatigue have essential function in modulating activity when the body is in a state of disease as in ME/CFS.

NICE, however, recommends over-riding this essential safety-net, thus the risk of serious harm is increased in this situation of simultaneous activity and symptoms denial. This will become a more serious risk in patients with more severe ME/CFS. The Guideline does not indicate how the clinician can tell whether patients' beliefs concerning their symptoms are aberrant and/or when the symptoms accurately point to the underlying state of the disease process"

**Dr Neil Abbot**
**Hon Research Fellow, Department of Medicine**
**University of Dundee**
**29th August 2008**

"There have been only five trials of CBT with a validity score greater than 10, one of which was negative for the intervention; and only three RCTs of GET with a validity score greater than 10. The total number of available trials is small; patient numbers are relatively low; no trial contains a 'control' intervention adequate to determine specific efficacy, and their results are relatively modest. In addition, some of the studies (particularly those on GET) have used the Oxford criteria for diagnosis, a rubric which allows selection of patients with chronic fatigue states and which do not necessarily exclude certain psychiatric disorders, raising the question of the applicability of the results of these studies to the many patients with specific biomedical symptoms and signs consistent with myalgic encephalomyelitis. Again, the heterogeneity of the trials, the potential effect of publication or funding bias for which there is some evidence, and professional doubts about the evidence base for some behavioural therapies themselves give grounds for caution as regards the usefulness of (CBT/GET). A commentary in the BMJ (Bolsover 2002) is particularly relevant: 'Until the limitations of the evidence base for CBT are recognised, there is a risk that psychological treatments in the NHS will be guided by research that is not relevant to actual clinical practice and is less robust than is claimed'. Indeed, a large body of both professional and lay opinion considers that these essentially adjunctive techniques have little more to offer than good medical care alone"

**Professors Nancy Klimas and Mary Ann Fletcher**
**University of Miami**
**13th September 2008**

"The overall flavour of the Guideline is to lump together all patients with 'medically unexplained fatigue', from relatively mild to profoundly disabling illness and to treat all patients with a standard approach of gradual reconditioning and cognitive behavioural modification. By lumping such a heterogeneous mix of patients…patients with CFS or ME are left with very limited options, and little hope.

In addition, this document proscribes immunological and other biologic testing on patients with (ME)CFS in the UK, despite the evidence in the world's medical literature that such testing produces most of the biomedical evidence of serious pathology in these patients.

Equally unfortunate is the GDG's recommendation for behavioural modification as the single management approach for all 'medically unexplained fatigue'.

This month we participated in the International Conference on Fatigue Science in Okinawa, Japan. Dr Peter White of the UK presented his work using behavioural modification and graded exercise. He reported a recovery rate of about 25%, **a figure much higher than seen in US studies in (ME)CFS and, even if possible, simply not hopeful enough to the 75% who fail to**

**recover"**

"Many of the symptoms of (ME)CFS are inflammatory in nature. There is a considerable literature describing immune activation in (ME)CFS. Overall the evidence has led workers in the field to appreciate that immunologic abnormalities are a characteristic of at least a subset of (ME)CFS and that the pathogenesis is likely to include an immunologic component.

Friedberg et al (2000) suggest the long duration (ME)CFS subjects are more likely to have symptoms suggestive of chronic immune activation and inflammation.

**Martin Bland, Professor of Health Statistics**
**University of York**
**17th September 2008**
"My main concern about the NICE document is that what must be great uncertainty in both costs and particularly in quality of life difference is not allowed for"

**Dr Layinka Swinburne, Leeds**
**22nd October 2008)**
"I am a consultant immunopathologist and before retirement worked at St James' University Hospital, Leeds. A key area of my professional interest was and remains myalgic encephalomyelitis and I have carried out research into the disorder. For a number of years I ran clinics specifically for patients with ME.

In my opinion NICE guidelines overemphasise the usefulness of CBT and GET to the detriment of patients. **I have no hesitation in stating that in my opinion, the situation for ME/CFS patients is worse, not better, since the publication of the NICE Guideline"**

**Dr Sarah Myhill,**
**General Practitioner specialising in ME/CFS**
**Powys; Secretary of the British Society for Ecological Medicine**
**10th November 2008**
"As my clinical freedoms were progressively eroded, it meant that I was becoming ineffective and indeed possibly dangerous as a practitioner.

All that patients could be offered was CBT coupled with GET, which I consider not to be appropriate for many of my patients and in the case of GET potentially damaging for some"

These comments by experienced ME experts and the fact that patients forced NICE to a judicial review does itself dictate that the guidelines need to be reviewed.
There is no confidence in them in the patient community.
The NICE guidelines are not gold-standard – they are a valueless and ineffectual set of biased dogma that benefit no one other than those who have vested interests in maintaining that ME is a behavioural condition.
An organisation such as NICE that purports to be "committed to promoting equality, eliminating unlawful discrimination, and actively considering the implications of its guidance for human rights" and yet is taken to court by the same patients for whom it claims to promote good healthcare –

this is an organisation that deserves to be overhauled, or removed.

**More Research**
Light et al. (2009) state that **symptoms experienced by CFS (ME) patients become markedly worse after exercise and "**After moderate exercise, CFS and CFS-FMS patients show enhanced gene expression for receptors detecting muscle metabolites and for SNS and IS, which correlate with these symptoms. These findings suggest possible new causes, points for intervention, and objective biomarkers for these disorders". [**7**]

Newton et al. (2010) established the relationship between the functional impairment experienced by Chronic fatigue syndrome (CFS) patients and the symptoms frequently experienced by those with CFS; specifically cognitive impairment, fatigue and orthostatic symptoms. They found that treatment of orthostatic symptoms in CFS has the potential to improve functional capacity and so improve quality of life. [**8**]

heedy at al. (2009) suggest "a probable link between intestinal colonization of Gram positive facultative anaerobic D-lactic acid bacteria and symptom expressions in a subgroup of patients with CFS. Given the fact that this might explain not only neurocognitive dysfunction in CFS patients but also mitochondrial dysfunction, these findings may have important clinical implications". [**9**]

**Serological Testing**
The NICE guideline for CFS/ME **proscribes** serological testing for infections yet there is new evidence of viral involvement in this group of patients. The studies on xenotropic **murine leukemia virus-related virus** (XMRV) show conflicting results but the cohorts, methodology and collection and storing of blood samples is not the same in all of these studies so one cannot just base one's views on the number of positive studies against the negative ones without addressing these issues. Moreover the positive studies supporting XMRV and murine leukemia virus (MLV)-related virus findings were published in high impact publications the Science magazine (*Lombardi et al*. 2009) and PNAS (*Lo et al*. 2010) adding weight to their importance.[**10**]

*The importance of gastrointestinal symptoms in CFS/ME and the known ability of enteroviruses to cause gastrointestinal infections led John and Andrew Chia to study the role of enterovirus infection in the stomach of CFS/ME patients…They describe a systematic study of enterovirus infection in the stomach of 165 CFS/ME patients, demonstrating a detection rate of enterovirus VP1 protein in 82% of patients…the possibility of an EV outbreak…seems unlikely, as these patients developed their diseases at different times over a 20 year period" [**11**]*

Chia et al. have followed patients with acute hospitalised febrile infections and screened them for enteroviruses and found that those who go on to develop ME show enteroviral persistence in their antrum years later (*Chia et al. 2008)*[**12**]

In Norway Naess et al. aimed to compare patients reporting acute infection with those reporting no infection at onset of chronic fatigue syndrome (CFS). The study included 873 patients with CFS who were referred to a tertiary centre on average 4.8 years after symptom onset. The assessment was by both observer query and self-reports. Antibody analyses against infectious agents including Epstein-Barr virus and enterovirus were performed in a majority of patients. Females comprised 75.3% of the patient group, and the mean age was 33 years. Initial infection was reported by 77%. There was no difference as to antibody analyses. Logistic regression showed that initial infection was independently associated with acute onset of fatigue, improvement of fatigue at referral, and the following symptoms at referral: fever, tender lymph nodes, and myalgia. CFS patients with initial infection as a precipitating factor more often reported acute onset of fatigue, more frequent accompanying symptoms, and more frequent improvement on referral than did patients without initial infection. (Naess et al. 2010) [**13**]

A recent study from Dundee University points to viral infection showing increased oxidative stress and increased white blood cell apoptosis in paediatric patients with ME. [**14**]

The request by NICE not to screen for infections therefore needs to be reviewed.
This alone requires a review of the NICE guidelines.

**Clinical area 3: Management of CFS/ME**

NICE asked if the evidence showed that any particular intervention or combination of interventions is effective in treatment, management or rehabilitation of adults and children with a diagnosis of CFS/ME and states that it identified studies were related to interventions for management of CFS/ME, focused on cognitive behavioural therapy (CBT).It referred to the FINE trial. It stated that in terms of pharmacological and dietary interventions, new evidence was identified however this was not contradictory to current guideline recommendations and evidence related to complementary therapies remains limited in quantity and quality. It states there is currently no new published evidence that would invalidate current guideline recommendations.

The problem regarding management lies in the lack of separation of ME from the various fatigue states which NICE seem happy to live with under one definition.

Patient surveys have suggested that graded exercise, which is a component of CBT, was felt to be the type of treatment that made more people with CFS worse than any other. A possible reason for negative patient reaction to these graded exercise strategies is suggested in a study by Jammes, Steinberg, Mambrini, Bregeon, and Delliaux, which found that incremental exercise among individuals with CFS was associated with oxidative stress and marked alterations of muscle membrane excitability. [**15**]

The Belgian government evaluated the outcome of the treatments at the CFS Centres. They concluded that a "rehabilitation therapy" with CBT/GET yielded no significant efficacy in the treatment of ME/CFS and that CBT/GET cannot be considered to be curative therapies. In case reports, it was shown that patients who were "treated" at those CFS centres with CBT/GET in fact suffered from IO&NS disorders, including intracellular inflammation, an increased translocation of gram-negative enterobacteria (leaky gut), autoimmune reactions and damage by O&NS." [**16**]

Twisk and Maes invalidated the (bio)psychosocial model for ME/CFS and demonstrated that the success claim for CBT/GET to treat ME/CFS was unjust. CBT/ GET was not only barely more effective than non-interventions or standard medical care, but many patients reported that the therapy had affected them adversely, the majority of them even reporting substantial deterioration. This review showed that exertion and thus GET most likely would have a negative impact on many ME/CFS patients. Exertion induces post-exertional malaise with a decreased physical performance/ aerobic capacity, increased muscoskeletal pain, neurocognitive impairment, "fatigue", and weakness, and a long lasting "recovery" time. This can be explained by findings that exertion may amplify pre-existing pathophysiological abnormalities underpinning ME/CFS, such as inflammation, immune dysfunction, oxidative and nitrosative stress, channelopathy, defective stress response mechanisms and a hypoactive hypothalamic-pituitary-adrenal axis. Twisk and Maes concluded that it was unethical to treat patients with ME/CFS with ineffective, non-evidence-based and potentially harmful "rehabilitation therapies", such as CBT/GET. - Twisk and Maes commented on CBT and GET in 2009 [**17**]

Even arch-proponent of CBT Professor Simon Wessely has himself stated on record that CBT doesn't work for all: in his he stated that CBT and GET are only "*modestly effective*" and that neither is "*remotely curative*" [**18**]

The recommendation of CBT and GET for ME was wrong in 2007 and it is wrong now.

There is little unequivocal evidence to show that CBT or GET has good evidence of benefit and much which shows the contrary result. Most of these studies have also used the flawed Oxford criteria for selection of participants in the programme where neurological symptoms of the illness disqualify patients from being included!

An important paper that was published in 2005 (well within the 2004 – 2007 life of the GDG's deliberations) demonstrated that exercising muscle is a prime contender for excessive free radical generation, free radicals being highly reactive molecules which can cause damage to the cells of the body. Incremental exercise challenge induces a prolonged and accentuated oxidative stress, and existing evidence has shown a good correlation between muscle pain thresholds on exercise with various blood markers of oxidative injury. This was not considered by NICE in the guidelines and therefore still has a bearing on this clinical area.[**19**]

The recommended graded exercise plan specifies that the intensity of GET should be incrementally increased, leading to aerobic exercise. This is in direct contradiction to international ME experts such as Professor Paul Cheney from the US, who in 1999 explained why aerobic exercise should not be used: "*The most important thing about exercise is not to have them do aerobic exercise. I believe that even progressive aerobic exercise, especially in phase one and possibly in other phases, is counter-productive. If you have a defect in the mitochondrial function and you push the mitochondria by exercise, you kill the DNA" [**20**]*

Professor Cheney has made a particular study of cardiac anomalies in patients with ME since the 1980s and emphasises the unassailable tenet that if metabolic demand (as in aerobic exercise) exceeds the impaired cardiac output of ME patients, even very briefly, **the result is death**.
This information was submitted to NICE and was available to the GDG, including the evidence that 82% of ME patients have abnormal cardiac impedence and that patients have a high heart rate but a low cardiac output caused by a problem with energy production, with ischaemic changes in the inner ventricular wall.

If a patient has abnormal oxygen consumption, muscles will not have enough oxygen and exercise will result in relapse. Patients' ability to work is impaired, as shown unequivocally by an abnormal serial exercise stress test which is 100% objective.

This information was ignored by the GDG but impacts upon the recommended management regime.

At this time there is no evidenced-based proof that these therapies are appropriate which has been accepted as rigorous and independent from the psychosocial approach to ME by some experts.

**REMAINDER OF CONSULTATION REVIEW DOCUMENT - Guideline Development Group and National Collaborating Centre perspective**

The rest of the consultation review document refers to trials CBT and GET therapies. It also briefly mentions "Conflicting evidence on the association between retrovirus and CFS/ME" but considers it outside the remit of the original guideline. It states that no identified new evidence contradicts current guideline recommendations and that the majority of respondents felt that there is insufficient variation in current practice supported by adequate evidence at this time to warrant an update of the current guideline.

We need to address the major flaw in the NICE guidelines – namely its bias toward promoting a predetermined one-size fits all approach to ME by continually highlighting CBT and GET therapies despite widespread derision from ME patients.

The Guideline acknowledges the Canadian Consensus Definition yet ignores its message; Dr Bruce Carruthers, Fellow of the Canadian Royal College and principle lead of the international expert team that produced the highly respected ME Clinical Case Definition, states in the Overview:
*"A hypothesis underlying the use of Cognitive Behaviour Therapy (CBT) for ME is based on the premise that the patient's impairments are learned due to wrong thinking and 'considers the pathophysiology of CFS to be entirely reversible and perpetuated only by the interaction of cognition, behaviour, and emotional processes. The patient merely has to change their thinking and their symptoms will be gone. According to this model, CBT should not only improve the quality of the patient's life, but could be potentially curative'. Supporters suggest that 'ideally general practitioners should diagnose CFS and refer patients to psychotherapists for CBT without detours to medical specialists as in other functional somatic syndromes'. Proponents ignore the documented pathophysiology of ME, disregard the reality of patient's symptoms, blame them for their illness and withhold medical treatment. Their studies have often included patients who have chronic fatigue but excluded more severe cases as well as those who have other symptoms that are part of the clinical criteria of ME. Further, their studies fail to cure or improve physiological impairments…"*

It should not be forgotten that after a course of CBT, there is no objective evidence of improvement (only subjective) and that the transient gains may be illusory as stated by Whiting et al. in their systematic review in. (JAMA 2001) [**21**]

NICE state that "*CBT is used as part of the overall management for many conditions, including cardiac rehabilitation, diabetes and chronic pain.*"
Yet we compared the NICE guidelines for other illnesses such as MS, Parkinson's etc. and showed NICE to be disingenuous at best.

For Dementia [CG42 Dementia NICE]

> *Carers of people with dementia who experience psychological distress and negative psychological impact should be offered psychological therapy, including cognitive behavioural therapy, conducted by a specialist practitioner. For people with dementia who have depression and/or anxiety, cognitive behavioural therapy, which may involve the active participation of their carers, may be considered as part of treatment.*
>
> **No GET was found.**

For Epilepsy [CG20 Epilepsy NICE]

> *Psychological interventions (relaxation, cognitive behaviour therapy, biofeedback) may be used in conjunction with AED therapy in adults where either the individual or the specialist considers seizure control to be inadequate with optimal AED therapy.*
> *Psychological interventions (relaxation, cognitive behaviour therapy) may be used in children with drug resistant focal epilepsy.*
> **No GET was found**

For MS [CG8 Multiple Sclerosis NICE]

> *Specific antidepressant medication, or psychological treatments such as cognitive behavioural therapy, should be considered, but only as part of an overall programme of depression management.*
> **No GET was found**

For Parkinson's [CG35 Parkinson's NICE]

**No mention of CBT or GET**

However, compare the above with conditions which are for mental health and behavioural conditions and one can see the following -

CG51 Drug misuse: psychosocial interventions: NICE guideline

*Cognitive behavioural therapy and psychodynamic therapy*
*Cognitive behavioural therapy and psychodynamic therapy focused on the treatment of drug misuse should not be offered routinely to people presenting for treatment of cannabis or stimulant misuse or those receiving opioid maintenance treatment.*

*Evidence-based psychological treatments (in particular, cognitive behavioural therapy) should be considered for the treatment of comorbid depression and anxiety disorders in line with existing NICE guidance for people who misuse cannabis or stimulants, and for those who have achieved abstinence or are stabilised on opioid maintenance treatment.*

CG22 Anxiety: NICE guideline

*Cognitive behavioural therapy (CBT) should be used.*
*CBT should be delivered only by suitably trained and supervised people who can demonstrate that they adhere closely to empirically grounded treatment protocols.*
*CBT in the optimal range of duration (7–14 hours in total) should be offered.*
*For most people, CBT should take the form of weekly sessions of 1–2 hours and should be completed within a maximum of 4 months of commencement.*
*Briefer CBT should be supplemented with appropriate focused information and tasks.*
*Where briefer CBT is used, it should be around 7 hours and designed to integrate with structured self-help materials.*
*For a few people, more intensive CBT over a very short period of time might be appropriate.*

This clearly showed the disingenuous intentions behind the NICE guidelines when they have applied them to a neurological illness such as ME.

There are therefore serious ethical concerns about whether this type of therapy is 'acceptable to Society', as well as outstanding safety issues. Where are the safeguards for this form of treatment? The guidelines maintain a deafening silence on these issues.
Drugs undergo exhaustive testing over an extended period of time overseen by an independent body thus ensuring their safety and efficacy. Comprehensive information on the intellectual foundation of the treatment, its effects and counter effects are provided to clinicians and patients. In the US, '*It takes 12 years on average for an experimental drug to travel from lab to medicine chest. Only five in 5,000 compounds that enter preclinical testing make it to human testing. One of these five tested in people is approved*.'. Similar rigorous testing processes apply to the UK under European Community regulations. The MHRA UK Regulatory Authority website states:

'Safety, quality and efficacy are the only criteria on which legislation to control human medicines is founded where experts assess all applications for new medicines to ensure they meet the required standards. This is followed up by a system of inspection and testing which continues throughout the lifetime of the medicine. Safety monitoring is also continuous and the doctors and patients receive up-to-date and accurate information about their medicines. This is achieved by ensuring that product labels, leaflets, prescribing information and advertising meets the required standards laid down by the Regulations.'.

Contrast the intellectual and scientific rigour applied in the approval process for the licensing of

drugs for clinical use, with the lack of scientific and intellectual rigour applied in the NICE guidelines with regard to the recommendations for the use of Psychological Therapy in CFS/ME. When compared with the extensive clinical trialling over many years and the independent scrutiny a drug therapy is subjected to, the small and heavily criticised evidence base used to justify the recommendation of CBT and GET for CFS/ME in the NICE guidelines is seen to be totally inadequate.

The report on ME from the Chief Medical Officer of 2002 stated that 65% of patients trialled using CBT found that it was of no value. An even more alarming figure of 50% stated that GET had made them worse. Reference was also made to a more recent study on CBT [**22**] which had failed to demonstrate any major overall benefit when CBT was compared to either education and support or standard medical care. Results from the trials listed by NICE even show the poor results from CBT.

- *13% were made worse by CBT, 32% were not helped at all, 37% were helped a little and 18% were helped a lot.' (Report on Survey of Members of Local ME Groups, Cooper 2000)*
- *93% found CBT unhelpful. (25% ME Group, Analysis Report, 2004)*

This is unequivocal - CBT is unhelpful. Yet still NICE persist in enforcing this on patients.

In a survey of 3074 ME patients conducted between 1998 – 2001, 55% of patients said that CBT had made no difference to their illness, whilst 22% said CBT had made their illness worse. 16% of patients said that Graded Exercise had made no difference to their illness whilst 48% said it had made their illness worse.

A survey by the 25% ME Group (for severe sufferers) of 437 patients, demonstrated that of the 39% of group members who had used graded exercise, 95% had found this therapy unhelpful, with most reporting their condition had been made worse by graded exercise. Some patients were not severely ill with ME until after graded exercise.
In the same survey - those who had undergone Cognitive Behavioural Therapy had found it unhelpful.

Professor Kenny De Meirleir – a researcher and physician with great experience of treating people with ME around the world - mentioned [**23**] that in trials in Belgium only 6% of patients found CBT helpful – and that a placebo would have given better results!

The amount of space given to CBT shows the lack of vision in this document, the lack of analysis carried out on biomedical research available and the true agenda behind NICE and this document.

NICE describe CBT as "a specific psychological therapy, based on underlying theoretical principles, with a broad evidence base across a variety of conditions".

NICE are not really aiming to treat the underlying pathology in any way.

Professor Malcolm Hooper says that CBT experts themselves have stated that any improvement from CBT is not sustainable.

NICE state that "*These are evidence statements agreed by the GDG, based on the evidence*

*reviewed."*
This calls into question the veracity and capability of the GDG and again shows the NICE spin as it has ignored valid evidence showing the lack of effect of CBT.

*NICE stated that "The aim of the CBT was to enable patients to address negative beliefs regarding symptoms, self-expectations and self-esteem. GET was tailored to each patient's physical capacity and aimed for a gradual increase in aerobic activities, especially walking, and was delivered by physiotherapists"*
*and*
"*Explaining the CBT approach in CFS/ME, such as the relationship between thoughts, feelings, behaviours and symptoms, and the distinction between causal and perpetuating factors.*"

and

"*CBT for a person with CFS/ME should be planned according to the usual principles of CBT, and should include: Challenging thoughts and expectations that may affect symptom improvement and outcomes.*"

This was revealing and shows the true nature and purpose of these guidelines. To associate a neurological illness with comments such as ' attempt to modify thoughts'. Is this the type of CBT which is given to cancer and diabetes patients?
Again NICE force upon patients the same old psychiatric therapies that it has just stated are not mandatory! It again lets slip its true agenda by concentrating on feelings and behaviours – straight from the psychiatrist's text book!

**GET**
NICE recommendations for using GET for showed a totally irresponsible and blinkered and biased approach to treating people with ME. Abundant research has at the very least cast serious doubt on its effects. ME patient groups reject its usage. But NICE refuses to listen and carries on with its dedicated agenda to enforce psychiatric paradigms on a vulnerable section of the community using policy-based evidence selection. How can a recovery be an objective with the use of GET when the causes of ME are 'unknown'?
NICE are totally discredited with these tactics.

Graded Exercise Therapy (GET) has been shown to be harmful or useless yet it is wrapped up into a psychiatric paradigm to allow vested interests to perpetuate the same old myths about ME.

The guidelines explicitly state that "*There was strong agreement that persistent, debilitating, post exertional fatigue characterised the condition*" - yet the Guidelines still recommend GET as a therapy/treatment.

"*An evidence-based approach to CFS/ME that involves physical assessment, mutually negotiated goal-setting and education.*"

There is poor quality evidence submitted by NICE to justify this claim and much evidence to the contrary which has been excluded.

GET is a proposed self-management technique that is not appropriate for patients with severe ME, where post-exertional oxidative stress can cause more serious problems.

"*Increases in duration of exercise*" are very dangerous, as blood pressure can drop and patients can be subject to numerous adverse reactions to any forced exercise. "*Aiming towards recovery*" implies that recovery is possible with increased exercise, which is unproven and fallacious.

A blanket recommendation of graded exercise therapy is imprudent for such a heterogeneous

group of patients (NICE "*there is growing evidence that the condition is heterogeneous, and may not have a single or simple aetiology*") most of which are likely to respond negatively to physical activity.

Of particular concern is a mounting body of evidence that shows that
exercise or over-exertion can worsen the health of ME sufferers and that, as such, GET has the potential to induce relapse, rather than being an effective recuperative therapy.
GET, as practiced today with ME patients, does not take into account a patient's preferences.
How can a recovery be an objective with the use of GET when the causes of ME are unknown? Yet this is what the NICE guidelines disingenuously propose.

There has been much research on muscle and immune cells. Christopher Snell in 2005 reported that the results of exercise capacity and immune function in male and female patients with CFS "implicate abnormal immune activity in the pathology of exercise intolerance in CFS and are consistent with a channelopathy involving oxidative stress and nitric oxide-related toxicity". This could explain why people with ME can't exercise, as there is a limit, beyond which one cannot train.

Lane et al have found evidence of abnormal muscle physiology in a significant number of ME patients that could not be explained by physical de-conditioning or muscle disuse.
Jammes et al make a connection between such muscle dysfunction and increases in oxidative stress observed in people with ME when subjected to incremental increases in exercise activity, a finding corroborated by Nijs et al.

Magnetic Resonance Imaging (MRI) brain scans compared between control patients and patients with ME indicated areas of reduced blood flow - indeed, myalgic encephalomyelitis might be a good name for such "brain-muscle" anomalies.

Professor Malcolm Hooper takes this one step further by making the association between increased oxidative stress and generation of free-radicals. Given the link between free-radicals, aging and cancer this is surely a matter of particular concern for those with ME. To put things succinctly, excessive exertion has the potential to cause premature aging and increased risk of cancer in those with ME.

The work of Chia establishes a link between enterovirus re-activation through over-exertion (exercise is mentioned as a specific example). This itself further supports the work of Lane who states -
"we have correlated abnormal lactate responses to exercise with the detection and characterisation of enterovirus sequences in muscle."

It is therefore possible to state that over-exertion by those with ME has the potential to lead to enterovirus re-activation as a result of faulty muscle metabolism.

An additional concern involves measurable cardiac insufficiency in those
with the illness. Peckerman et al have demonstrated a link between symptom severity and cardiac dysfunction. This work is backed up by that of Vanness, Snell et al, who go so far as to state that:
"The blunted heart rate and blood pressure responses in the `mild' through `severe' groups are similar to those seen in chronic heart failure."

It is also worth noting that in their study, they accounted for any potential "lack of effort" on the part of their subjects:
"it was felt that the multiple testing protocol employed in this study was sufficient to ensure that the results obtained accurately reflect patients' functional capacities."

With regard to cardiac function and exercise therapy, Carruthers and van de Sande issue the following warning:
"Externally paced `Graded Exercise Programs' or programs based on the premise that patients are misperceiving their activity limits or illness must be avoided."

Thus we have several health risks for those with ME which may be
exacerbated by exercise: excessive oxidative stress and resultant generation of free-radicals, enterovirus reactivation, and cardiac dysfunction.

All three have the potential to cause serious harm, and arguably have lethal potential.

Given this situation, it is surely irresponsible to recommend exercise therapy for this particular patient group.

Every medication has to have a list of side-effects – these need to be stated here also with reference to GET. GET needs to carry a government health warning for ME patients.
As NICE continue to recommend GET then they have to shoulder some of the responsibility for the consequences. In light of the evidence presented, it is possible that use of GET for those with ME will ultimately be self-defeating. By increasing the risk of relapse and increasing overall health risks rather than reducing them, it is dangerous for patients and risks increasing the burden of illness posed by ME on society at large. Page 28/52

The weight of empirical evidence indicates that exercise has direct and persistently negative impacts on the physiology and quality of life of a significant subgroup of ME patients. Any universally applied therapy is unlikely to address the heterogeneity of ME, and graded exercise is particularly unsuitable as it may worsen the condition, and should not be generally recommended without a high degree of confidence that it will not be applied to susceptible patients.

It is difficult to conceive of a more inappropriate therapy for ME.

By increasing the risk of relapse and overall health risks, rather than reducing them, graded exercise therapy also risks increasing the burden of illness on society at large.

The present review suggests that an approach based on treatment of the underlying physiological dysfunction will be more fruitful.

NICE chose to ignore what patients say about CBT and GET.

**Human Rights**

The recommendation from NICE to use psychological therapies for treating ME contravenes the human rights of patients with ME.

It has been stated that by ignoring the serious issues with regard to CBT and GET the NICE guidelines would violate the right of clinicians and patients to the highest, safest standards of medical practice and care, amounting to a violation of their Human Rights, apart from major concerns about the efficacy of use of CBT or about the danger in the use of GET.

There is no regulatory framework governing the development and use of CBT and GET thus leaving ME patients vulnerable to exploitation and abuse at the hands of the vagaries of power, politics

and prejudice.

IiME would state that this is already the case, as frequent letters to our information mailbox attest to this fact.

In respect of informed consent for using these therapies the issue does not arise.

There simply cannot be informed consent since there are important ethical, safety and regulatory questions arising from these treatments, to be addressed.

Ethical and safety questions such as those raised in the MRC Neuroethics Report 2005 should be paramount.
It is hard to envisage any Independent authority clearing a drug for Human testing or use without ethical and safety issues, like those surrounding Psychological Therapy, being resolved.

By ignoring these serious issues with regard to Psychological Therapy the NICE guidelines violate the right of clinicians and patients to the highest, safest standards of Medical practice and care, amounting to a violation of their Human Rights.
This is a Human Rights issue.

Without an answer to whether this type of therapy is 'acceptable to Society' and if it is, without an effective Regulatory framework governing its development and use, there is the serious risk that sick and vulnerable people everywhere will be vulnerable to exploitation and abuse at the hands of the vagaries of power, politics and prejudice.

NICE (its chairman and CEO and the chair of these guidelines) should be accountable in a court of law for any harm done to patients given these treatments/therapies.

**FINE Trials**
The FINE Trial which received £1,147,000 of Medical Research Council funding did not result in inconclusive findings as stated by NICE. The results were negative and do not give any support for such an intervention to be used in the management of ME patients.

The FINE Trial abstract concluded: " For patients with CFS/ME in primary care, pragmatic rehabilitation delivered by trained nurse therapists improves fatigue in the short term compared with unconstrained GP treatment as usual, but the effect is small and not statistically significant at one year follow-up. Supportive listening delivered by trained nurse therapists is not an effective treatment for CFS/ME."[**24**]

**VIRUSES**
There can be no dismissing the evidence of viral involvement in ME, much of which pre-dated the PACE Trial.

Research studies have identified various features relevant to the pathogenesis of CFS/ME such as viral infection, immune abnormalities and immune activation, exposure to toxins, chemicals and pesticides, stress, hypotension and neuroendocrine dysfunction.

The NICE guidelines proscribe serological testing for infections yet there is new evidence of viral involvement in this group of patients. The studies on XMRV have dominated the discussion around ME in the past year forcing a shift in approach to this disease. So much so that many countries have banned patients with ME from donating blood. In the UK the ban is said to be to protect the patient from getting worse in other countries it is due to safeguarding the blood supply from potential retrovirus contamination.

**XMRV**

**The CRD states "**Conflicting evidence on the association between retrovirus and CFS/ME were also highlighted. However, this is considered outside the remit of the original guideline.**"**

Yet the original guidelines document was entitled
**"Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): diagnosis and management of chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy) in adults and children"**

It is insufficient for the NICE GDG to claim that consideration of the retroviral association with CFS/ME did not come within its remit – it was charged with providing guidance on the diagnosis of "CFS/ME", so any research which demonstrates a biomedical aetiology should have form part of the literature review, and the guidance review.
NICE recommend that viral serology should not be carried out in the absence of a recent history suggesting viral infection as it was "*difficult to establish a link between CFS/ME and serology indicating past viral infection, and that serological evidence of past infection would not alter the patient's management*".

In the early stages of illness it is important to identify viral or bacterial causes and treat them early with relevant antimicrobials.

**In the CDR document** "The original scope is inclusive of diagnosis, treatment and management of mild, moderate or severe CFS/ME in children (aged 5 years and upwards, including young people in transition to adulthood) and adults."

So it is entirely valid for the latest XMRV research to be included in a review document and cannot be considered to be outside the remit of the official guidelines unless the GDG takes the view that evidence of XMRV infection is exclusionary for the diagnosis of ME.

The Science paper [**25**] published in 2009 discovered XMRV in blood and showed a possible association between the retrovirus and ME.

**XMRV is a member of the same family of retroviruses as the AIDS virus. A retrovirus inserts itself into the host's genetic material by copying its genetic code into the DNA of the host by using RNA and once there, it stays for the life of the host.**

If there is now evidence of viral association then it is inherent on NICE to review that information with regard to diagnosis and management as the present NICE guidelines proscribe serological testing of people with ME.

This statement alone would negate the recommendation of the GDG.

Dr Judy Mikovits – Research Director at the Whittemore-Peterson Institute –

***""Neurological maladies and immune dysfunction with inflammatory cytokine and chemokine up-regulation are some of the most commonly reported features associated with CFS…The presence of infectious XMRV in lymphocytes may account for some of these observations of altered immune responsiveness and neurological function in CFS patients.***
***"In summary, we have discovered a highly significant association between the XMRV retrovirus and CFS.***
***"This observation raises several important questions. Is XMRV infection a causal factor in the pathogenesis of CFS or a passenger virus in the immunosuppressed CFS patient population?…Conceivably these viruses could be co-factors in pathogenesis, as is the***

***case for HIV-mediated disease, where co-infecting pathogens play an important role. Patients with CFS have an elevated risk of cancer."***

**"***Since the original Science paper was submitted, we have continued to refine our test for XMRV and have surprisingly found that 95% ME samples tested positive for XMRV antibodies in the plasma. 'This finding clearly points to the retrovirus as a significant contributing factor in this illness'* ***said Judy Mikovits, director of research for WPI.***
*This landmark study was the first to isolate XMRV particles from the blood and show that it can be transmitted between blood cells. Researchers have confirmed that this retrovirus is transmitted through body fluids and is not airborne"[26]*

The NIH National Cancer Institute's press release ("Consortium of Researchers Discover Retroviral Link to Chronic Fatigue Syndrome") said:

***"Scientists have discovered a potential retrovirus link to chronic fatigue syndrome….****'We now have evidence that a retrovirus named XMRV is frequently present in the blood of patients with CFS. This discovery could be a major step in the discovery of vital treatment options for millions of patients'* ***said Judy Mikovits, leader of the team that discovered this association….The virus, XMRV, was first identified by Robert H Silverman, professor in the Department of Cancer Biology at the Cleveland Lerner Research Institute…****The research team not only found that blood cells contained XMRV but also expressed XMRV proteins at high levels and produced infectious viral particles****…These results were also supported by the observation of retrovirus particles in patient samples when examined using transmission electron microscopy. The data demonstrate the first direct isolation of infectious XMRV from humans….****Retroviruses like XMRV have also been shown to activate a number of other latent viruses. This could explain why so many different viruses…have been associated with CFS****. Dan Peterson, medical director of WPI, added:** *'Patients with CFS deal with a myriad of health issues as their quality of life declines. I'm excited about the possibility of providing patients who are positive for XMRV (with) a definite diagnosis and, hopefully very soon, a range of effective treatment options'* **"[***27***]***

This requires NICE to recognise that the research landscape has changed and needs to be reflected in diagnosis and management, and possibly treatment.

There have been no true replication studies published in literature yet. Lo and Alter say they practically confirmed WPI results but it was not a replication study in the true sense of the word.

Such is the seriousness with which this research has been viewed that it is the subject of major reviews in healthcare policy in ISA and other countries.

NICE recommend that viral serology should not be carried out in the absence of a recent history suggesting viral infection as it was "*difficult to establish a link between CFS/ME and serology indicating past viral infection, and that serological evidence of past infection would not alter the patient's management*".

In the early stages of illness it is important to identify viral or bacterial causes and treat them early with relevant antimicrobials. With the possibility of XMRV playing a role in ME it is even more important.

**Blood Ban for People with ME**

The XMRV research has caused Australia, New Zealand, Canada and UK to have banned people from ME from donating blood. In the UK this is a permanent lifetime prohibition even if the patient

has "recovered".

It is perverse for NICE to state that this is outside the remit of the original guideline.

**THE BENEFITS of IMMUNOGLOBULIN**

In its Implementation and post publication feedback NICE state that for immunoglobulin therapy no new evidence was identified through post publication enquiries or implementation feedback that would indicate a need to update the guideline.

Dr Irving Spurr [**28**] states that the following-

> IgG may work via a multi-step model where the injected IgG first forms a type of immune complex in the patient. Once these immune complexes are formed, they interact with activating Fc receptors on dendritic cells which then mediate anti-inflammatory effects helping to reduce the severity of the inflammatory state and potential for autoimmune disease [PTF and Diabetes]
>
> IgG also blocks the antibody receptors on immune cells (macrophages), leading to decreased damage by these cells, or regulation of macrophage phagocytosis.
>
> IgG may also regulate the immune response by reacting with a number of membrane receptors on T cells, B cells, and monocytes that are pertinent to autoreactivity and induction of tolerance to self.
>
> A recent report stated that IgG application to activated T cells leads to their decreased ability to engage microglia. As a result of IgG treatment of T cells, the findings showed reduced levels of tumour necrosis factor-alpha and interleukin-10 in T cell-microglia co-culture. The results add to the understanding of how IgG may affect inflammation of the central nervous system in autoimmune inflammatory diseases.

**SUMMARY**

The reasons why the draft Guidelines were almost universally condemned was due to the poor quality of analysis and their lacking ability to serve the needs of people with ME and their families. **With these guidelines for ME NICE failed people with ME and their families. NICE also failed healthcare professionals.**

Invest in ME believe that so much has changed with regard to ME since the NICE guidelines were published that a review is the very least that NICE should offer.

These NICE guidelines are a poor collection of outdated theories and attempts at treatment. They do nothing to help either GPs or patients deal with this illness.

They add nothing to improve the situation for patients whose lives are being wasted without any sign of a radical change in the way biomedical research into ME is initiated.

They fail the severely affected people with ME by offering them nothing but a referral to specialist

care.
NICE fail to define what this specialist care means.

Looking at the aims and objectives with these guidelines it is clear one can come away with only one conclusion.
Revision is mandatory.

Failure and dissatisfaction now seem to be synonymous with NICE and it seems that NICE are constantly in opposition with what patients and patient groups need and want.
Why this constant misrepresentation is occurring with NICE is something the government ought to look in to.
Certainly the management at NICE seem to attract attention for all of the wrong reasons.

Any decision not to review the NICE guidelines should augur the removal of any role for NICE in future guidance provision for ME, and perhaps indicate that NICE itself should be reviewed and terminated.

**If there are any areas excluded from the original scope that you feel need to be addressed in any update decision, please write these in the box below**

NICE state that "*The research recommendations were chosen to prioritise those areas that would most directly inform future guidelines.*"

Yet no biomedical research is highlighted which will help future guidelines.
The current and previous biomedical research is seemingly ignored.
The literature searches referred to by NICE seemingly failed to find the abundance of biomedical research into ME and we wonder whether they were conveniently ignored?

We cannot accept that these guidelines still use as broad a section of fatigue states as possible in describing ME.

*NICE did not take into account the biomedical research evidence from around the world which indicated that ME is of an organic nature.*
*This was clearly highlighted in the Gibson Inquiry of 2006.*
*There was no excuse to ignore the biomedical research and the NICE guidelines remain permanently flawed due to the biased approach of the GDG.*
Other cogent criticisms of the draft NICE Guideline included one submitted by a member of the Association of British Neurologists:

*"The draft guideline is fundamentally flawed because it presupposes certain interventions (CBT and GET) to be highly effective in CFS/ME for routine clinical use despite lack of adequate evidence. The Guideline is also selective in its review of existing literature and is heavily influenced by (the) psychiatric view of the condition. Indeed, it almost seems that a select group of psychiatrists with a polarised view of this complex condition is directing the development of the guideline from 'behind the scene'. There has been no review of general and post-exercise pain. The draft guideline reflects an incomplete and psychiatrically polarised view of CFS/ME. The importance of appropriate diagnosis of CFS/ME from common psychiatric conditions has not been mentioned even once. No-where in this guideline have the exclusion criteria for CFS/ME (e.g. generalised anxiety disorder, somatisation) been adequately defined and properly discussed. The guideline needs to be thoroughly revised to reflect our current understanding of this condition rather than the supposition of the psychiatrists. It would be immoral for NICE not to recognise the huge dissatisfaction about this draft guideline amongst most patients, carers and clinicians. The guideline should not re-define CFS/ME to 'fit in' CBT and GET as the recommended treatment options. Listen to patients".*

We dispute the continued characterisation of ME as being '*poorly understood*'. There are over 4000 biomedical publications on the illness which the NICE searches should have seen and analysed.

Views by ME support groups show that ME must be seen as a distinct and separate illness from CFS as described by NICE and the CDC empirical definition. This, we feel, is part of the problem with healthcare staff and others – by broadening the view of what ME is it will inevitably dilute the requirements for diagnosing and treating ME patients.

The guidelines are a quite biased and narrow-looking report which mixes up far too many illnesses and research information simply to prove the original intention of the document – to force people with ME to be given psychological therapies and repeat the myths of the past.

It also attempts to subjugate ME into a bag of common illnesses all falling under the term CFS. In this NICE have done a major disservice to people with ME who are needlessly suffering from the perceptions of biased healthcare professionals who maintain their views with little good scientific evidence.

This questions the impartiality of NICE and the Guidelines.

NICE state that "*The research recommendations were chosen to prioritise those areas that would most directly inform future guidelines.*"

Yet no biomedical research is highlighted which will help future guidelines.
The current and previous biomedical research is seemingly ignored.
The literature searches referred to by NICE seemingly failed to find the abundance of biomedical research into ME and we wonder whether they were conveniently ignored?

We cannot accept that these guidelines still use as broad a section of fatigue states as possible in describing ME.

**Epidemics**
The NICE guidelines do not carry one reference to epidemics despite strong evidence to support this from numerous references.
Why?
NICE failed to make any changes to the draft guidelines in this respect and ignored IiME's questions relating to this despite IiME supplying at least 12 references as evidence.
Why?

**Organo-Phosphate poisoning**
The NICE guidelines do not carry any reference to organo-phosphate poisoning despite the evidence indicating it being linked to ME.
Why?
These are all major oversights by NICE.
IiME consider that these links are important and should at least be included in any serious review of the bio-medical situation for patients who present with conditions similar to ME.

IiME suggests that research ought to be performed on historical evidence from epidemics and vaccinations that have resulted in similar conditions to ME and the NICE GDG ought to have analysed these topics sufficiently to include comment as the information can directly affect diagnosis and management.

**Severely Affected**
NICE state that "*No definitive studies have been carried out in the UK to determine the prevalence of severe CFS/ME in people with CFS/ME*".
Would it not be possible to extrapolate these figures from those statistics of people claiming incapacity and DLA benefit due to ME?

**Sub Grouping**
We need to subgroup CFS/ME so that ME is separate from the various fatigue states which have so benefited the psychiatric lobby and their unscientific trials and so rewarded them with the near totality of available funding.

The guidelines ask " *What are the best ways of sub grouping patients to aid in diagnosis and management?*" and then fail to discuss sub grouping or even mention it again.
NICE make no mention of the need for sub-grouping of the current ME patients and separation from chronic fatigue.

Professor Leonard Jason of DePaul University, Chicago published in 2005 an excellent review on the need for sub-grouping of the over-broad "diagnostic category" CFS which can catch widely different groups of patients in its net. As he said,

*"This review suggests that there is a need for greater diagnostic clarity and that this might be accomplished by subgroups that integrate multiple variables including genetic, neurological, psychological and biological domains."*

To quote Dr. Vance Spence of ME Research UK

"This illness is very big, very complicated and we are not going to solve anything by pushing everyone in to one large group called CFS At present, what patients are left with is a "devalued" diagnosis consisting of (in one researcher's words) a "*...ragbag of common non-specific symptoms with many causes, mistakenly labelled as a syndrome"*."

This is a major failing of NICE as no recommendation on sub grouping is made. The guidelines fail to address a key element in the treatment of this illness and so fail all ME patients as well as healthcare staff.
Sub-grouping is indeed one of the big issues and NICE could have done more by calling for this to happen and basing the sub-grouping on up-to-date and valid criteria for diagnosis such as the Canadian guidelines.

**Human Rights**
As sated earlier the emphasis on CBT and GET for treating people with ME is a violation of human rights and this subject has been completely ignored by NICE ,

**Supplements and Alternative Medicines**
The NICE guidelines provide an incredibly poor and limited summary on supplements as aids in managing ME.
Supplements are dismissed with little research or attempt to analyse.
Yet they can be a useful part of the diet for patients who cannot cook always or who cannot eat properly and could benefit from such supplements (fish oils, vitamin C, multi-vitamins etc.) - surely this is a negligent oversight from NICE.
In terms of supplements, two "essential fatty acids" studies had positive results and very high rankings - 16 and 17 respectively. Carnitine, liver extract, and magnesium also scored as high as CBT in terms of therapies (10, 10, and 15).
The highest validity scores in the data presented by NICE was for an alternative therapy.
Fish oils score as highly or better than CBT so why does NICE not recommend this as a therapy/treatment?

**AGREE Standards**

The AGREE Instrument (Appraisal of Guidelines Research and Evaluation Instrument) with which NICE is obliged to comply in the formulation of all its Guidelines is specific: "*The health benefits, side effects and risks should be considered when formulating the recommendations".*

NICE failed to conform to the AGREE Instrument which requires that NICE is obliged to give equal weight to three main sources of data: "evidence-based" medicine, usually deemed to be random controlled trials (RCTs); the opinion and experience of physicians with expertise in the area, and the opinion and experience of the patient group for whom the Guideline is intended.

NICE did not abide by the European AGREE standards which govern guideline development.

**If there are any equality issues relevant to the guideline that you do not feel have been adequately addressed please write these in the box below**

The CFS/ME guideline 53 put forward a psychosocial model for ME and promoted CBT and GET as the only options for management. The biological model with evidence of inflammatory, immune, oxidative and nitrostative pathways as key areas was ignored.

As Maes and Twisk (*BMC Medicine 2010, **8:**35*) point out in their review of the 'biopsychosocial' model put forward by Harvey and Wessley [**29**] -

"Interventions with CBT/GET are potentially harmful for many patients with ME, since the underlying pathophysiological abnormalities may be intensified by physical stressors."

The guideline should be changed to make sure that no harm is caused to patients by inappropriate prescribing of CBT and GET.

A further submission from the Association of British Neurologists said the following:

*"(The Guideline Development Group) is tactically promoting Oxford criteria over the more widely used and recognised international CDC criteria – again, a clear evidence of psychiatrists' influence on this group".*

Referring to a paragraph in the draft Guideline: *"This paragraph deals with a publication (Wessely et al, Lancet 1999) which was published as a HYPOTHESIS and which remains to be proven. However, the GDG seems to have taken it as a matter of fact. Please refer to the criticisms of this article in the Lancet. Being only a hypothesis, (it) is totally irrelevant for the purpose of a dedicated guideline on CFS/ME".*

*"The GDG should also be criticised for its total lack of reference to the neurological aspect of fatigue and its overemphasis and over-reliance on the psychiatric literature from a group of psychiatrists".*

*"With the possible exception of some psychiatrists, most specialists prefer the international criteria to diagnose CFS/ME".*

*"Clearly there is very little compelling evidence at present that these patients benefit from CBT and GET".*

*"There is selective omission of research literature on reproducible neuroendocrine tests, with an overemphasis on research data from certain psychiatrists".*

**INVEST in ME REFERENCES**

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Syndrome
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Thes following organisations were approached but did not respond:

Action Against Allergy
Action Heart
Airedale NHS Foundation Trust
Alder Hey Children's NHS Foundation Trust
Alder Hey Children's NHS Foundation Trust
Anglesey Local Health Board
Arrhythmia Alliance
Assist Trauma Care
Association for Cognitive Analytic (ACAT) Therapy
Association For Family Therapy and Systemic Practice in the UK (AFT)
Association For Family Therapy and Systemic Practice in the UK (AFT)
Association for Psychoanalytic Psychotherapy in the NHS (APP)
Association of British Neurologists
Association of NHS Occupational Physicians
Association of Psychoanalytic Psychotherapy in the NHS
Association of the British Pharmaceuticals Industry (ABPI)
Association of Young People with ME
Avon and Wiltshire Mental Health Partnership NHS Trust
Avon and Wiltshire Mental Health Partnership NHS Trust
Avon and Wiltshire MHP NHS Trust
Barnsley PCT
BASRaT (British association of Sports Rehabilitators and Trainers
BMJ
British Association for Behavioural & Cognitive Psychotherapies (BABCP)
British Association for Community Child Health
British Association for Counselling and Psychotherapy
British Association of Drama Therapists
British Association of Psychodrama and Sociodrama (BPA)
British Association of Sport and Exercise Medicine
British Dietetic Association
British Homeopathic Association
British Infection Association (formerly Association of Medical Microbiologists)
British Infection Association (formerly British Infection Society)
British Medical Association (BMA)

British National Formulary (BNF)

British Paediatric Mental Health Group

British Paediatric Mental Health Group of the Royal College of Paediatrics and Child Health

British Pain Society

British Psychodrama Association

British Psychological Society, The

British Society for Clinical Neurophysiology

British Society of Paediatric Gastroenterology, Hepatology & Nutrition (BSPGHAN)

Buckinghamshire PCT

Buckinghamshire PCT

BUPA

Calderdale PCT

Cambridge University Hospitals NHS Foundation Trust (Addenbrookes)

Cambridgeshire & Peterborough Mental Health Trust

Care Quality Commission (CQC)

CFS/ME Clinical Network Coordinating Centre

Chartered Society of Physiotherapy (CSP)

Chronic Fatigue Research Unit at King's College London

Cochrane Depression, Anxiety & Neurosis Group

College of Mental Health Pharmacy

College of Mental Health Pharmacy

College of Occupational Therapists

Community Practitioners and Health Visitors Association

Connecting for Health

Cornwall Acute Trust

Counselling and Psychotherapy Trust (registered charity No. 1063175)

County Durham & Darlington Priority Services NHS Trust

David Lewis Centre, The

Defence Medical Services Directorate (MOD)

Department for Communities and Local Government

Department for Work and Pensions

Department of Health Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI)

Department of Health, Social Services & Public Safety, Northern Ireland (DHSSPSNI)

Devon Partnership NHS Trust

Doctors Support Network

Eli Lilly and Company Ltd

Epsom-St. Helier University Trust Chronic Fatigue Service

Faculty of Occupational Medicine

Faculty of Occupational Medicine

Ferring Pharmaceuticals Ltd

Gedling Primary Care Trust

Gibson Parliamentary Inquiry into ME/CFS

Good Hope Hospitals NHS Trust

Greater Manchester West Mental Health NHS Foundation Trust

Guildford & Waverley Primary Care Trust

Hampshire Partnership NHS Foundation Trust

Health Protection Agency

Healthcare Quality Improvement Partnership

Hertfordshire Partnership NHS Trust

Human Givens Institute

Humber NHS Foundation Trust
Kent & Medway NHS and Social Care Partnership Trust
King's College London
Lancashire Care NHS Foundation Trust
Leeds PCT
Liverpool PCT
LocalME
Maidstone and Tunbridge Wells NHS Trust
Manchester Mental Health & Social Care Trust
ME Research UK (formerly MERGE - Myalgic Encephalomyelitis Research Group for Education and Support)
Medicines and Healthcare Products Regulatory Agency (MHRA)
ME-letterforce National e-group
Mid Staffordshire General Hospitals NHS Trust
Ministry of Defence (MoD)
National CAMHS Support Service
National CFS Network Executive Committee
National CFS/ME Observatory
National Institute for Mental Health in England (NIMHE)
National ME Centre, The
National Patient Safety Agency (NPSA)
National Treatment Agency for Substance Misuse
National Tremor Foundation
National Youth Advocacy Service
NCC - Cancer
NCC - Mental Health
NCC - National Clinical Guideline Centre (NCGC)
NCC - Women & Children
Newcastle PCT
NHS Bedfordshire
NHS Clinical Knowledge Summaries Service (SCHIN)
NHS Direct
NHS Fife
NHS Milton Keynes
NHS Plus
NHS Quality Improvement Scotland
NHS Sheffield
NHS Western Cheshire
North Eastern Derbyshire PCT
North Glamorgan NHS Trust - Merthyr Tydfil
North Staffordshire Combined Healthcare NHS Trust
North West Wales ME_FM Support Group
North Yorkshire and York PCT
Northern Ireland Campaign for ME/CFS
Northumberland, Tyne & Wear NHS Foundation Trust
Nottinghamshire Acute Trust
Nottinghamshire Healthcare NHS Trust
Nutrition Society
One Click Group
Oxford Nutrition Ltd
Oxfordshire & Buckinghamshire Mental Health Partnership NHS Trust
Pain Concern
Partnerships for Children, Families, Women and Maternity
Pelvic Pain Support Network

Peninsula Primary Care Psychology & Counselling Services
PERIGON Healthcare Ltd
Pottergate Centre for Dissociation & Trauma
PPG group (paediatric/psychiatric pharmacology group)
Primary Care Pharmacists' Association
Primary Care Rheumatology Society
PRIME Project
Princess Alexandra Hospital NHS Trust
Public Health Wales
Queen Elizabeth Hospital NHS Trust (Woolwich)
Rotherham NHS Foundation Trust
Rotherham Primary Care Trust
Royal College of Anaesthetists
Royal College of General Practitioners
Royal College of General Practitioners Wales
Royal College of Midwives
Royal College of Obstetricians and Gynaecologists
Royal College of Pathologists
Royal College of Physicians London
Royal College of Psychiatrists
Royal College of Radiologists
Royal College of Surgeons of England
Royal National Hospital For Rheumatic Diseases
Royal Pharmaceutical Society of Great Britain
Royal Pharmaceutical Society of Great Britain
Sacyl
Scarborough and North Yorkshire Healthcare NHS Trust
Scottish Intercollegiate Guidelines Network (SIGN)
Sensory Integration Network
Sheffield Children's NHS Foundation Trust
Sheffield PCT
Sheffield Teaching Hospitals NHS Foundation Trust
Sigma-tau Spa
Sky Medical Technology Ltd
Social Care Institute for Excellence (SCIE)
Society for Academic Primary Care
Society for Endocrinology
Solent Healthcare
South & Central Huddersfield PCTs
South Essex Partnership NHS Foundation Trust
South Tees Hospitals NHS Trust
South West Alliance for ME (SWAME)
Southampton City Council
Staffordshire Moorlands PCT
Stockport PCT
Tees Esk & Wear Valleys NHS Trust
The Neurological Alliance
The Robert Jones & Agnes Hunt Orthopaedic & District Hospital NHS Trust
The Royal Society of Medicine
The Royal West Sussex Trust
The South Asian Health Foundation
UK Anaemia
UK Specialised Services Public Health Network

University Hospital Aintree
Urgo Medical Ltd
Vasomedical Inc.
Welsh Assembly Government
Welsh Scientific Advisory Committee (WSAC)
Wessex Neurological Centre
West London Mental Health NHS Trust
Western Cheshire Primary Care Trust
York Teaching Hospital NHS Foundation Trust