National Institute for Health and Clinical Excellence

Review of Clinical Guideline (CG53) – Chronic fatigue syndrome/ myalgic encephalomyelitis (or encephalopathy): diagnosis and management of chronic fatigue syndrome, myalgic encephalomyelitis (or encephalopathy) in adults and children.

Stakeholder Comments

Please enter the name of your registered stakeholder organisation below. **NICE is unable to accept comments from non-registered organisation or individuals. If you wish your comments to be considered please register via the NICE website or contact the registered stakeholder organisation that most closely represents your interests and pass your comments to them.**	
Stakeholder Organisation:	**Invest in ME**
Name of commentator:	**Kathleen McCall**
Do you agree with the proposed review decision?	~~YES~~/NO NO

If no, please add any reasons/comments in the box below

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 review document provides sparse information on the discussions behind the 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 [**30**]
"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."

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**]

Sheedy 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 of 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 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.

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 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 USA 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 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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