

Stakeholder Response to NICE CG53 Three Yearly Review

East Anglia ME Patient Partnership (EAME)

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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]. Indeed, in his witness statement to the High Court dated 21 July 2008, Dr Ian Gibson, NICE CG53 Stakeholder and Chairman of the parliamentary Group on the Scientific Research into ME (GSRME) stated:

"I do not believe that the NICE CFS/ME Guidelines are fit for purpose."[2]

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. Thus, in his witness statement to the High Court of 23 June 2008, Dr Terry Mitchell, one of the country's most experienced Specialist ME/CFS NHS Hospital Consultants and CNCC stated:

"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.”[3]

Neither in the opinion of many experienced professionals did NICE properly assess all of the international scientific data on ME/CFS (see below). In the aforementioned witness statement Dr Mitchell therefore also states:

“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.”

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.

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. Let 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/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 [50-55] 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 an 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/xmrvi/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/s12026-010-8165-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

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www.agreecollaboration.org/instrument/

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[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:

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[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:

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[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.

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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:

www.litemiami.com/spotlite/index.aspx

www.pandoronet.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 – ISBN: 92 4 154649 2.*
- *International Statistical Classification of Diseases and Related Health Problems - Tenth Revision – Second Edition: Volume 2 – Instruction Manual – ISBN: 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_Classification_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.

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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)

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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

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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:

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[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]:
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[178] See the High Court witness statements of Dr Bruce Carruthers-

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[179] See the High Court witness statements of Dr Professor Malcolm Hooper-

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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 days per week for 12 weeks | + | 9 |
| 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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[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