

**REPORT: COMPLAINT TO THE RELEVANT EXECUTIVE EDITOR OF  
THE LANCET ABOUT THE PACE TRIAL ARTICLES PUBLISHED BY THE  
LANCET**

**Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded  
exercise therapy, and specialist medical care for chronic fatigue syndrome  
(PACE): a randomised trial** PD White et al

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(FAST TRACKED)

and

**Chronic fatigue Syndrome: where to PACE from here?** G Bleijenberg and H  
Knoop

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(with grateful acknowledgment to members of the ME/CFS community)

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**PREAMBLE**

In 1996 when psychiatrists Drs. Peter White and Simon Wessely co-authored a review of “Chronic Fatigue Syndrome” (Joint Royal Colleges Report, CR54, October 1996), a Lancet editorial roundly condemned the publication (“Frustrating survey of chronic fatigue”, Volume 348, Issue 9033, Page 971, 12 October 1996): *“Psychiatry has won the day for now .... The sixteen-strong committee was top-heavy with psychiatric experts, so the emphasis on psychological causes and management is no surprise .... We believe that the report was haphazardly set-up, biased, and inconclusive, and is of little help to patients or their physicians”*.

In 2011, when Professors White and Wessely collaborated in a multi-centre trial of cognitive behaviour therapy and graded exercise for “CFS”, peer review at The Lancet failed to identify the same faults. “Psychiatry has won the day” again - but only because once again the same people have not been subjected to sufficiently rigorous scientific scrutiny.

## **INTRODUCTION**

This report deals with the results of the PACE Trial published in The Lancet in the following sections:

1. Terminology and Classification
2. Fast track publication
3. The competing interests of the PACE Trial team
4. The Principal Investigators were not studying classic ME/CFS
5. Failure to comply with professional ethical guidance and codes of practice
6. Failure to “control” the PACE Trial
7. Adverse events/reactions and serious deterioration
8. Changes to the entry criteria
9. Consideration of the data on outcomes
10. Data not reported/measures dropped
11. Overview of reporting results
12. Announcement of results to press at the Science Media Centre
13. Summary/Conclusion.

Having served as an examiner in UK and other universities at graduate and postgraduate level, acted as referee for a number of scientific journals and served on an editorial Board, and having served on the Committee of the Council for National Academic Awards and also of the World Health Organisation, it is my professional opinion, based on the extensive published biomedical evidence about myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and supported by over 2,000 pages of evidence obtained under the Freedom of Information Act (FOIA), that the PACE Trial itself was unethical and unscientific: the Investigators had already formed their opinion about the intended outcome; entry criteria were used that have no credibility; definitions and outcome measures were changed repeatedly; data appears to have been manipulated, obfuscated, or not presented at all (so it cannot be checked), and the authors’ interpretation of their published data as “moderate” success is unsustainable.

Significant problems with the PACE Trial were identified from the outset and were brought to the attention of the Medical Research Council (a co-funder), who for over eleven months failed to respond. The concerns thus became the subject of at least two separate formal complaints at Ministerial level. A formal complaint about the West Midlands Multicentre Research Ethics Committee (MREC) that approved the PACE Trial Protocol was also served on the National Research Ethics Service (NRES) at the National Patient Safety Agency.

The Lancet has published a report of a study about which legitimate and serious concerns were raised that are centred on apparent coercion and exploitation of patients; on the contempt in which patients are seen to be held; on manipulation; on pretension and misrepresentation; on reliance on flawed studies yielding meaningless results; on the remarkable lack of scientific rigour throughout the trial; on the unusual personal financial interest of the Chief Principal Investigator (whose own money funded the PACE Trial entry criteria); on the vested interests of all the Principal

Investigators, of the Director of the PACE Clinical Trial Unit and of the centre statistician; on the intentional inclusion of patients who do not suffer from the disorder supposedly being studied; on the lack of individual equipoise, and the failure to adhere to CONSORT (Consolidated Standards of Reporting Trials), to the Department of Health Research Governance Framework for Health and Social Care, Second Edition, 2005; 2:3:1; to the General Medical Council “Good Practice in Research” and “Consent to Research”, and to the Declaration of Helsinki (which is clear: ***“Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research....Reports of research not in accordance with the principles of this Declaration should not be accepted for publication”***).

On the basis of evidence seen, the underlying non-clinical purpose of the trial had the primary aim of removing patients from benefits (ie. the use of motivational behaviour therapy to achieve the intended result of the cessation of State/insurance benefits for patients with ME/CFS), as those involved with the trial continue to maintain that for people with ME/CFS, ***“medical intervention is no longer appropriate”*** and that the aim of therapy is to ***“reduce healthcare usage”*** ([http://www.meactionuk.org.uk/Problems and Solutions.htm](http://www.meactionuk.org.uk/Problems_and_Solutions.htm)).

In one of the MRC secret files about ME/CFS held at the National Archives in Kew (files that are closed for an unusually lengthy period of 73 years instead of the customary 30 years, some of which have been legally obtained), one of the Principal Investigators (PIs) of the PACE Trial (Professor Michael Sharpe), admitted that CBT and GET were ***“a purely pragmatic approach and without theoretical foundation”*** (CIBA Foundation Symposium, 12<sup>th</sup>-14<sup>th</sup> May 1992, reference S 1528/1). Particularly notable is that the same document states about ME/CFS patients: ***“The first duty of the doctor is to...avoid the legitimisation of symptoms and reinforcement of disability”***. Avoiding the legitimisation of the symptoms of ME/CFS was considered by many to be the purpose of the PACE Trial.

The Manuals used in the PACE Trial show that the authors either ignored medical science or that they do not understand medical science. The Manuals describe behaviours and techniques that should not -- and I believe cannot -- be considered ethical by any independent and reasonable observer, particularly the intense pressure on both therapists and participants to obtain the “right” results for the PIs and their funders (pressures that are supported by participants’ published comments). Much of the written information and instruction to therapists and doctors is contradictory and internally inconsistent and appears highly exploitative, as well as revealing an ignorance of ME/CFS.

One of the substantive complaints to the Minister about the PACE Trial can be accessed at <http://www.meactionuk.org.uk/magical-medicine.htm> and it addresses in detail the numerous ethical and scientific failures of the study.

As Chief Principal Investigator, Professor Peter White was aware of these complaints and in the interests of transparency and under the requirement for disclosure had a duty to bring them to the attention of The Lancet editorial staff before publication of the PACE Trial results, which he failed to do.

For The Lancet to have published an article reporting a study that completely ignored the existing biomedical evidence-base of over 4,000 published papers about the disorder allegedly studied, including documented physiological contra-indications regarding aerobic exercise, is a matter of concern to the international scientific community, as it is in defiance of basic principles of scientific research.

It also contravenes the Elsevier Editorial System (Ethics in Publishing: Instructions to Authors) which, under “Ethics and Procedures (General)”, sets out its “fundamental principles” that ***“the paper should....be appropriately placed in the context of prior and existing research”***.

Indeed, the UK Department of Health, a co-funder of the PACE Trial, stipulates that: ***“All existing sources of evidence...must be considered carefully before undertaking research”*** (Research Governance Framework for Health and Social Care, Second Edition, 2005; 2:3:1).

Not only did White et al ignore the international biomedical evidence-base pertaining to ME/CFS, whilst in their article they make reference to the FINE Trial (Fatigue Intervention by Nurses Evaluation, a sibling of the PACE Trial), they do not point out that it failed (BMJ 2010:340:c1777), and they also failed to take due cognisance of the mixed evidence-base about the efficacy of CBT/GET which shows that those interventions are not effective in general and specifically that they may be harmful for people with ME/CFS. Feedback from almost 5,000 ME/CFS patients via several charities indicates that deterioration following exercise is reported in almost 50% of cases and indeed, in 2002 the Chief Medical Officer’s Working Group Report highlighted the disparity between feedback from patients and the reported findings of the Wessely School (see below), stating: ***“...the data clearly indicate that the York review results (of controlled trials) do not reflect the full spectrum of patients’ experience”***.

Nine years later, the £5 million PACE Trial (at a cost of £7,500 per participant) takes us no further forward, as safe guidance on management options must address the needs of *all* patients with ME/CFS. The PACE Trial excluded those more severely affected by ME/CFS (since including such patients would have greatly reduced any apparent benefit of the interventions), so it is not the case that the PACE Trial results are generalisable to all people with the disorder as claimed by the authors.

It is essential that the findings of the PACE Trial are properly identified, interpreted and presented. The most pressing concern is that the findings published in The Lancet will be deemed appropriate for all people with ME/CFS, many of whom stand to suffer iatrogenic harm from incremental aerobic exercise because the findings of research conducted on the Oxford criteria (as used in the PACE Trial) cannot justifiably be applied to people with classic ME as recommended in The Lancet article, even with the authors’ caveat ***“only if fatigue is their main symptom”***.

Thus a major factor motivating this complaint is that, as a result of The Lancet article, it is highly likely, perhaps even inevitable, that patients with classic ME/CFS will be forced to undertake exercise regimes as “rehabilitation” on pain of losing their State benefits, which are often their sole means of financial survival. Such regimes are guaranteed to exacerbate the symptoms of an already very difficult-to-bear illness. In

such a situation, resort to suicide is not unimaginable and indeed already occurs with higher than normal regularity.

The President of the International Association for ME/CFS, Professor Fred Friedberg from Stony Brook University, New York, emphasised his concern about the take-home message from the press conference held at the Science Media Centre (where Professor Wessely, Director of the PACE Clinical Trial Unit, is on the Science Advisory Panel) which rapidly led to the spread of false information around the world, that message being: ***“Exercise is good; Rest is bad”***, because the evidence is that exercise regimes are ***“potentially harmful for patients with CFS/ME”***.

In his own press release, Professor Friedberg commented about the PACE Trial article in The Lancet: ***“The most fundamental concern we have is focused on the type of causal model that was linked to the CBT and GET conditions in this study. The model, based on the application of cognitive behavioural and physical deconditioning principles, predicts that properly designed behavioural or exercise interventions will ‘reverse’ the CFS illness. Not improve symptoms/functioning or provide better management, but ‘reverse’ the illness. This term implies that the illness can be cured (or something close to it) with behavioural techniques....If one assumes such a direct correspondence between behavioural treatment and curative outcomes, then the illness is by implication a psychiatric condition....Perhaps this is the most unfortunate aspect of the PACE trial: the omission of any reference to the medical complexity of this illness”*** (<http://www.iacfsme.org/PACETrial/tabid/450/Default.aspx> ).

In his closing remarks to an annual conference of about 300 civil servants on 3<sup>rd</sup> February 2011 held in London, the Government’s Chief Scientific Advisor (Professor Sir John Beddington CMG, FRS) said that pseudo-science ought to be considered in the same way as racism: ***“We are grossly intolerant, and properly so, of racism....We are not...grossly intolerant of pseudo-science, the building up of what purports to be science by the cherry-picking of the facts and the failure to use scientific evidence and the scientific method”*** ([http://www.researchresearch.com/index.php?option=com\\_news&template=rr\\_2col&view=article&articleId=1032320](http://www.researchresearch.com/index.php?option=com_news&template=rr_2col&view=article&articleId=1032320) ).

To have published the contrived results of what can only be described as pseudo-science is not only damaging to patients but also to The Lancet, as well as raising legal implications for clinicians who may rely on the published conclusions of the study and who might thereby be in breach of GMC regulations and of advice from the medical defence unions.

## **1. TERMINOLOGY AND CLASSIFICATION**

The Principal Investigators (PIs) of the PACE Trial, Professors Peter White, Michael Sharpe and Trudie Chalder, and the Director of the Clinical Trial Unit (Professor Simon Wessely, who oversaw the centre statistician) believe that the disorder they purported to be studying in the PACE Trial (myalgic encephalomyelitis/chronic fatigue syndrome, or ME/CFS) does not even exist (see Appendix 1).

They all belong to the Wessely School. The Wessely School (Hansard, Lords, 9<sup>th</sup> December 1998:1013) have for two decades used the terms “chronic fatigue”, “chronic fatigue syndrome”, “CFS”, “myalgic encephalomyelitis”, “ME”, and “CFS/ME” interchangeably. However, very recently, the Chief PI (Professor Peter White) and the Director of the Clinical Trial Unit (Professor Simon Wessely) have co-authored a paper in which they distinguish between chronic fatigue syndrome and chronic fatigue, which is a new departure that makes interpretation of the PACE Trial results even more confusing (BMC Medicine 2011; 9:26doi:10.1186/1741-7015-9-26).

ME has been classified by the WHO as a neurological disorder since 1969 (currently in WHO ICD-10 at G93.3, with “post-viral fatigue syndrome” as a synonym). Since 1992 “Chronic Fatigue Syndrome” (CFS) has been indexed only to G93.3 as an alternative name for ME, hence the use of the term “ME/CFS” adopted by The International Association of ME/CFS (although many international research papers use the single term “CFS”).

The international evidence-base is that ME/CFS is a serious, inflammatory multi-system disorder with well-documented abnormalities in the central nervous system, the autonomic nervous system, the cardiovascular, respiratory, neuroendocrine, immune and gastro-intestinal systems, with convincing evidence of muscle pathology, defects in gene expression, specific HLA antigen expression, and with irrefutable evidence of chronic inflammation.

Moreover, since 2008 the US Government (which co-funded the assay research with \$1 million) has, after eight years, accepted a specific assay as a proven biomarker for all autoimmune diseases which, according to some researchers, means it has been proven that ME/CFS is an autoimmune disease (Co-Cure: Research Discoveries; 20<sup>th</sup> March 2011).

By contrast, chronic “fatigue” (ie. a syndrome of chronic “fatigue”) is classified as a mental/functional/behavioural disorder in ICD-10 at F48.0. By letter dated 16<sup>th</sup> October 2001 the WHO confirmed that ME/CFS is specifically excluded from F.48.0 and ME/CFS is not included in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).

On 4th February 2009, Dr Robert Jakob, Medical Officer (ICD), Classifications, Terminologies and Standards, WHO Headquarters, confirmed: ***“CFS is a broad umbrella. This needs to be clarified. It is not possible to make a deduction from CFS. Volume I is the relevant volume for ME. 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. In its Guideline, NICE has used an ambiguous term. The WHO does not recognise the term ‘CFS/ME’ and refers to it as ‘unfortunate’ ”.***

However, the “PACE Trial Information” states: ***“Medical authorities*** (meaning the Wessely School themselves) ***have decided to treat CFS and ME as if they are one illness”***; they refer to “CFS/ME” in their publications and particularly in the Chief

Medical Officer's Working Group Report of January 2002 and in the NICE Clinical Guideline 53 of August 2007.

It is a matter of record that the Wessely School reversed the term ME/CFS to "CFS/ME" because they intend to drop the "ME" component from "CFS/ME" when they deem it expedient: *"It is only human for doctors to view the public as foolish, uncomprehending, hysterical or malingering....It may seem that adopting the lay label (ME) reinforced the perceived disability. A compromise strategy is 'constructive labelling'; it would mean treating chronic fatigue syndrome as a legitimate illness while gradually expanding understanding of the condition to incorporate the psychological and social dimensions"* (B Fischhoff, S Wessely. BMJ 2003;326:595-597).

It is noted that, whilst the PACE Trial literature refers to the term "ME", the title of The Lancet article omits all mention of it.

The Wessely School assert that "CFS/ME" is a functional disorder that is reversible by directive -- as distinct from supportive -- cognitive restructuring combined with incremental graded aerobic exercise, and that these interventions will return patients of working age to economic productivity (Occupational Aspects of the Management of Chronic Fatigue Syndrome: a National Guideline; NHS Plus, October 2006: DH Publications 2006/273539).

UK Government Ministers have repeatedly confirmed in writing and in Parliamentary debates (so are recorded in Hansard) that both they and the Department of Health accept not only the WHO classification of ME/CFS as a neurological disorder, but that ME/CFS is a neurological disorder. Since 2003 ME/CFS has been classified in the UK Read Codes used by all GPs as a neurological disease at F 286. (The code "F" relates to neurological disorders and should not be confused with the code "F" in the ICD, which relates to mental and behavioural disorders). The UK National Service Framework on chronic neurological conditions includes ME/CFS. There can thus be no doubt that ME/CFS is -- and is accepted to be -- a neurological disorder, not a mental disorder.

However, the MRC co-funded the PACE Trial and the MRC has for many years considered ME/CFS to be a mental disorder, as can be seen from the Report from a Working Group of the MRC's Neurosciences and Mental Health Board (NMHB) Strategy and Portfolio Overview Group (SPOG) of January 2005. Professor Wessely was a member of three MRC Boards, including the NMHB, and both he and the MRC consider CFS/ME to be a mental disorder: at paragraph 6.2 the Report is unequivocal: ***"Mental health research in this instance covers CFS/ME"***.

One of the many attempts of the Wessely School to reclassify ME/CFS as a mental disorder was thwarted when in September 2001 the WHO issued a statement repudiating the Wessely School's unofficial re-classification of this disorder as a mental disorder in the UK "Guide to Mental Health in Primary Care", saying that it was at variance with the WHO's position.

Not only has the WHO confirmed in writing that ME/CFS may not be moved from the neurological chapter or subsumed into any other classification category and that

ME/CFS is expressly excluded from classification as a mental disorder, it has confirmed that a dual classification of the same disorder in different chapters of the ICD is not permitted. Following the Wessely School's numerous assertions that the ICD-10 classified CFS in two different sections – once in the neurological chapter but also in the mental and behavioural disorders chapter -- their claim of dual classification was firmly rejected by the WHO, who on 23<sup>rd</sup> January 2004 (ie. before the PACE Trial started) provided written clarification: ***“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”.***

Dismissive of the WHO classification, another attempt to re-classify ME/CFS as a mental disorder was made by the Chief PI in his presentation to the Royal Society of Medicine Conference on “CFS” in April 2008, in which he was unequivocal in advising clinicians to ignore the ICD-10 classification:

***“I’m going to try to define what Chronic Fatigue Syndrome is. By doing so, I’m going to review the ICD-10 criteria for the illness and see if they’re helpful. The answer will be, they are not helpful.....This meeting is about clinicians making the diagnosis and helping patients.....Then we come the three clinical criteria to see if they’re useful, and two of them actually do have help to us: the NICE Guidelines criteria and the Royal College of Paediatrics and Child Health criteria I would commend to you”.***

For the avoidance of doubt, the NICE Guideline CG53 recommends CBT/GET and very limited investigations, whilst the RCPCH Report of December 2004 (Evidence-based Guidelines for the Management of CFS/ME in Children and Young People) bears little relationship to children and young people with ME/CFS. The College’s view of ME/CFS is that it is a behavioural disorder. The RCPCH report emphasised behavioural interventions: ***“Children and young people with CFS/ME should be considered for graded exercise or activity programmes”*** and contributors referred to the ***“emotional dimensions of the illness”***, stating: ***“The overarching aim of CBT is to help patients modify their behaviour for their own benefit”.***

White continued:

***“Does the ICD-10 help us? Unfortunately not; there are at least five ways of classifying CFS using the ICD-10 criteria. What are they? We start off well: myalgic encephalomyelitis is in the neurology chapter of ICD-10...and helpfully, “chronic fatigue syndrome, postviral”. So it starts off well [said sarcastically and in a mocking tone]. What if the viral illness is not a clear trigger for the illness? Well, you’ve got alternatives: in the Mental Health Chapter, you’ve got Neurasthenia...if you think that somehow, psychological factors have some role to play”.***

White then discussed the various somatoform classifications for chronic fatigue before saying:

*“the trouble with these diagnoses is, you somehow have to guess that psychological factors have an important role to play in their aetiology”.*

He concluded his presentation: *“It’s confusing, isn’t it?...ICD-10 is not helpful and I would not suggest, as clinicians, you use ICD-10 criteria. They really need sorting out, and they will be in due course, God willing”.*

That was a clear instruction to clinicians to disregard the ICD-10 classification of ME/CFS as a neurological disorder, adherence to which is mandatory: *“ICD-10 is used within the acute sector of the NHS and classification codes are mandatory for use across England”* (NICE: Communications Progress Report 8, 18<sup>th</sup> September 2002).

Key people in the PACE Trial have fixed beliefs that ME/CFS is a behavioural disorder. They have not kept up-to-date with ME/CFS biomedical research and have not changed their own beliefs for the last 25 years, and in defiance of the WHO, in the PACE Trial cohort the PIs intentionally conflated a nosological disorder with heterogeneous chronic fatigue, thereby constructing an unclassified and meaningless amalgam of their own creation, with the intentional inclusion of participants with at least three taxonomically distinct disorders: ME/CFS (coded to ICD-10 G93.3); fibromyalgia (coded to ICD-10 M79) and states of chronic fatigue or tiredness (coded to ICD-10 F48.0). This is not in accordance with the principles of scientific research, which require as homogeneous a cohort as possible in a clinical trial.

Furthermore, because of recruitment difficulties, on 14<sup>th</sup> July 2006 Professor Peter White (the Chief Principal Investigator) sought approval from the West Midlands MREC to advertise his PACE Trial to doctors and to ask them to refer anyone *“whose main complaint is fatigue (or a synonym)”* to enter the trial.

Such heterogeneity severely undermines the conclusions of the article that purports to be studying “CFS/ME” patients.

This lack of observance of taxonomic principles and consequent likelihood of inappropriate treatment of patients is also evident in the approach taken by the MRC (one of the co-funders of the trial).

## **2. FAST TRACK PUBLICATION**

Unless undue pressure was brought to bear by Professor White, it is unclear why the article was fast-tracked, particularly since (i) the article provides no new evidence that would be of benefit patients and (ii) the standard of the article is poor.

As long ago as 2001, Simon Wessely, Director of the PACE CTU, reported that CBT and GET are only *“modestly effective”* and that *“neither approach is remotely curative....These interventions are not the answer to CFS”* (Editorial: Simon Wessely JAMA 19<sup>th</sup> September 2001:286:11).

More recently, Wessely sounded a warning note: *“It should be kept in mind that evidence from randomised controlled 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”* (Huibers and Wessely. Psychological Medicine 2006;36:(7):895-900).

In 2008, a Cochrane review was lukewarm about the short-lived effects of these treatments (Price JR, Mitchell E, Tidy E, Hunot V. Cognitive behaviour therapy for chronic fatigue syndrome in adults. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD001027. DOI: 10.1002/14651858.CD001027.pub2.)

Thus White et al’s conclusion that the interventions are *“moderately effective”* provides no new evidence despite costing UK tax-payers £5 million.

### **3. THE COMPETING INTERESTS OF THE PACE TRIAL TEAM AND THE LANCET “COMMENT” AUTHORS**

*“All submissions to The Lancet must include disclosure of all relationships that could be viewed as presenting a potential conflict of interest – see Lancet 2001:358:854-856 and Lancet 2003:361:8-9”*: <http://www.thelancet.com/lancet-information-for-authors/statements-permissions-signatures#role-of-funding-source>

Broadly speaking, two issues are pertinent with regard to conflicts of interest and potential conflicts of interest here. One is the extent to which those involved have complied with the stipulated requirements to declare conflicts and potential conflicts of interest. The other is the need to assess the published article against the implications of any such conflicts of interest.

#### **PROFESSOR PETER WHITE**

Chief Principal Investigator psychiatrist Professor White has declared certain conflicts of interest in the Lancet publication:

*“PDW has done voluntary and paid consultancy work for the UK Departments of Health and Work and Pensions and Swiss Re (a reinsurance company)”*.

Prof White is in fact Chief Medical Officer for Swiss Re, a giant re-insurance company, and he is also Chief Medical Officer for Scottish Provident.

In November 2006 senior Parliamentarians found Professor White’s close financial involvement with the insurance industry *“to be an area for serious concern and recommends a full investigation by the appropriate standards body”* ([http://erythos.com/gibsonenquiry/Docs/ME\\_Inquiry\\_Report.pdf](http://erythos.com/gibsonenquiry/Docs/ME_Inquiry_Report.pdf)).

Those parliamentarians who expressed this concern included the former Chairman of a House of Commons Science and Technology Select Committee and former Dean of

Biology; a member of the Home Affairs Select Committee; a Minister of State for the Environment; a former President of the Royal College of Physicians; the Deputy Speaker of the House of Lords, and a former Health Minister and Honorary Fellow of the Royal College of Physicians.

Professor White also does paid and unpaid work for Universities, the UK Government, the United States Centres for Disease Control, and for legal claimants and defendants (BMC Health Services Research 2003:3:25) which were not declared in The Lancet article.

White is in fact lead advisor on “CFS/ME” to the Department for Work and Pensions and was a prominent member of the group who re-wrote the chapter on it in the DWP’s Disability Handbook used by Examining Medical Practitioners, by DWP decision-makers and by members of the Appeal Services Tribunals. It is the DWP’s known intention to remove as many people as possible from state benefits, and to this end ME/CFS (or CFS/ME) is a specifically targeted disorder. It is the case that the PACE Trial is the only clinical trial that the DWP has ever funded, and that the DWP had open access to participants’ medical records.

The entry criteria for the MRC PACE Trial were the Wessely School’s own criteria (Oxford 1991), which were funded in part by the Chief Principal Investigator’s own money (JRSM 1991:84:118-121), thus giving him an unusual interest in the outcome of the PACE Trial.

#### PROFESSOR MICHAEL SHARPE

Principal Investigator psychiatrist Professor Michael Sharpe has also declared conflicts of interest in The Lancet publication:

***“MS has done voluntary and paid consultancy work for government and for legal and insurance companies, and has received royalties from Oxford University Press”.***

Professor Sharpe is also heavily involved with the permanent health insurance industry, especially with UNUMProvident, whose track record is disturbing (see “The advent of UNUMProvident into the UK benefits system”: <http://www.meactionuk.org.uk/magical-medicine.htm> ).

Members of the Scottish Parliament have written to Allied Dunbar, another insurance company with which Professor Sharpe is involved, about their concerns over his suitability to give an unbiased view when assessing people with ME/CFS. Sharpe has asked MSPs to withdraw their statements to Allied Dunbar about him; the MSPs have not done so.

Sharpe is lead author of the paper setting out the Oxford entry criteria used in the PACE Trial.

### PROFESSOR SIMON WESSELY

Although not an author of The Lancet article, the Director of the PACE Clinical Trial Unit, psychiatrist Professor Simon Wessely, has a known association with the insurance industry and his role and influence bear examining in this context.

Regarding the commercial interests of the PACE Trial team, Simon Wessely was listed as a Corporate Officer in the PRISMA company information; he was a member of the Supervisory Board, and in order of seniority, he was higher than the Board of Management. PRISMA is a multi-national healthcare company working with insurance companies; it arranges “rehabilitation” programmes (ie. GET) for those claiming on their insurance policies and it claims to be especially concerned with long-term disability from the perspective of Government, service providers and insurance companies. According to Professor Michael Sharpe: ***“Funding of rehabilitation by commercial bodies has begun in the UK (with organisations such as PRISMA) and is likely to continue”*** (Functional Symptoms and Syndromes: Recent Developments. Trends in Health and Disability, UNUMProvident, 2002).

### PROFESSOR TRUDIE CHALDER

Former mental health nurse and Principal Investigator Professor Trudie Chalder declared:

***“TC has done consultancy work for insurance companies and has received royalties from Sheldon Press and Constable and Robinson”.***

However, Miss Chalder is also involved with the insurance industry in far more depth than is apparent from her brief declaration in the “Conflicts of Interest”. Her academic (as distinct from her mental nursing) career seems to have been devoted to promoting the interests of the insurance industry; indeed, at a Symposium on CFS entitled “Occupational Health Issues for Employers” held at the London Business School on 17<sup>th</sup> May 1995 on the insurance implications and at which attendees were informed that ME/CFS has been called ***“the malingerer’s excuse”***, Miss Chalder spoke on ***“Selling the treatment to the patient”***.

### JESSICA BAVINTON

Physiotherapist Jessica Bavinton declared:

***“JB was on the guideline development group of the National Institute for Health and Clinical Excellence guidelines for chronic fatigue syndrome and myalgic encephalomyelitis and has undertaken paid work for the insurance industry”.***

Miss Bavinton was in fact the primary author of the PACE Trial Graded Exercise Therapy manual, which in the October 2007 Declaration of Interests for the NICE

Guideline she declared her intention to publish, an intention which places her in the position of having a commercial interest in the outcome of the PACE Trial.

In common with the Principal Investigators, Ms Bavinton is heavily involved with the permanent health insurance industry. She works for more than three such companies, one being Scottish Provident, who by letter dated 7<sup>th</sup> August 2007 signed by Kenneth MacMahon stated in a letter to a claimant: ***“We are arranging for a claims visit. This will be done by Jessica Bavinton who specialises in performing home visits of this nature”***.

On 13<sup>th</sup> August 2007, in a (recorded) telephone conversation, Miss Bavinton herself has stated that she does ***“lots of these assessments for insurance companies”***.

There is a long and significant conflict of interest between patients with ME/CFS and the medical and permanent health insurance industry, details of which can be found in the substantive complaint referred to above. The indisputable commitment of so many members of the PACE team to the insurance industry (especially Professors White and Sharpe in their roles as Chief Medical Officer to so many insurance companies) is a significant cause for concern, since their continued recommendation of CBT and GET and their insistence that ME/CFS is a functional (mental) disorder benefits the insurance industry for which they work to the prejudice of patients.

The medical and permanent health insurance industry has a vested interest in ensuring that ME/CFS is regarded as a mental health disorder to enable it to be excluded from insurance cover ([http://erythos.com/gibsonenquiry/Docs/ME\\_Inquiry\\_Report.pdf](http://erythos.com/gibsonenquiry/Docs/ME_Inquiry_Report.pdf)). This results in a major conflict of interest on the part of the PACE Trial investigators, the extent of which is not discernable from the authors' disclosures in The Lancet article.

Thus the PIs have a considerable interest in ensuring that ME/CFS is denied legitimacy as an organic disorder; if accepted as such, it would cost their insurance company paymasters (and the Government departments which they advise) an inordinate amount of money.

That is the acknowledged ethos that underpinned the PACE Trial, which is one arm of a three-armed policy, the other arms being the “Fatigue” Clinics and the NICE Clinical Guideline 53 on CFS/ME, all of which are intended to deliver a nationwide programme of management using psychological strategies (Welsh Assembly Government Disclosure Log 2296).

Against this background, the previously published views of the PIs and of the Director of the CTU about ME/CFS assume greater significance, as does the highly questionable calibre of the article published in The Lancet.

#### DR TONY JOHNSON

The PACE Trial statistician and Deputy Director of the MRC Biostatistics Unit Dr Tony Johnson declared in the PACE trial article that he has no conflicts of interests.

However, Dr Johnson has long held very definite and disparaging views about people with ME/CFS.

For example, in his Quinquennial Report for the MRC's Biostatistical Unit's progress report for the years 2001 to 2006 that was placed on the MRC website (but now removed), Johnson wrote: "***The Unit's scientists must remain wary of patient-pressure groups. CFS is currently the most controversial area of medical research and characterised by vitriolic articles and websites maintained by the more extreme charities supported by some patient groups, journalists, Members of Parliament, and others, who have little time for research investigations***". Coming from such a senior figure within the MRC, and considering his level of involvement with the PACE Trial, Johnson's adverse and biased comments carried considerable authority and influence.

In his Report, Johnson referred dismissively to "***websites maintained by the more extreme charities***" but did not mention that it was two of the UK's major charities (The ME Association, which is the longest-established ME charity, and the 25% ME Group for the Severely Affected) that were calling for the PACE trial to be halted.

When challenged, Johnson admitted that he was unable to substantiate his assertion that some patient groups, journalists and Members of Parliament have little time for research investigations. By letter dated 7<sup>th</sup> November 2006 he attempted to exonerate himself, stating that the views he had expressed in his Quinquennial MRC Report were not intended to represent the views of the MRC.

In his MRC report, Johnson revealed that he had used data that he had been able to obtain through "***familial involvement with one of the charities***" to assist in the design of the PACE trial (his mother-in-law is Dr Elizabeth Dowsett, a former President of the ME Association). The CBT arm of the PACE Trial was about challenging ME/CFS sufferers' (correct) beliefs, so it is disturbing that Johnson used information he obtained through "***familial involvement with one of the charities***" to design a trial whose aim was to promote a management regime that, according to patients' statements, has already caused so much harm to members of that charity.

From Dr Johnson's report on the MRC website and the way it was handled by the MRC, the ME/CFS community was left in no doubt about the contempt for sufferers, for some ME/CFS charities, and for those MPs who support them at the MRC.

The role and background of Dr Tony Johnson are further considered on pages 409-413 at <http://www.meactionuk.org.uk/magical-medicine.htm>

#### COMMERCIAL PACKAGES IN RELATION TO THE FINE AND PACE TRIALS

In relation to the FINE Trial, by letter dated 24<sup>th</sup> June 2005, Alan Carter of The Directorate of Corporate Services at the University of Manchester stated: "***if the treatments under investigation in this Trial are successful, The University of Manchester would wish to develop training packages for use by PCTs (Primary***

*Care Trusts)*” and he specifically referred to his wish not to “*endanger the University’s commercial interests in developing treatment packages as detailed above*”.

It is understood that similar commercial packages exist in relation to the PACE Trial, which would be an undeclared vested interest on the part of the PIs.

### COMPETING INTERESTS ARE NOT LIMITED TO FINANCIAL CONFLICTS

In the case of the PACE Trial, too much professional credibility was invested in it for it to be allowed to fail.

Indeed, the CFIDS Association of American has commented about the PACE Trial that: “*It is difficult to ignore the UK government’s strong stake in a good outcome.... (The trial) was conducted for the benefit of making or revising health policy for the treatment of CFS by the National Health Service. It came at a cost of some £5 million pounds (British) or \$8 million (U.S.). In essence, it was too big to fail to reinforce existing UK policy that favours provision of psychological approaches over medical ones. It’s hard to imagine that it was worth \$8 million to obtain data on slim gains achieved in such an artificially constructed setting*” (Commentary on the PACE Trial. <http://www.cfids.org/cfidslink/2011/lancet-study.asp>).

The careers of Professors White, Sharpe and Wessely have been largely based on their own model of ME/CFS as a reversible behavioural disorder and too much is at stake for these Wessely School psychiatrists to be seen to have been proved wrong.

According to internationally acclaimed medical ethics expert Professor John Ioannidis: “*Hidden agenda bias occurs when a trial is mounted, not to answer a question, but in order to demonstrate a pre-required answer....Closely related to this is the self-fulfilling prophecy bias, in which the very carrying out of the trial ensures the desired result*”.

Many informed people have no reason to doubt that this is the kind of bias which pervaded the PACE Trial.

Ioannidis continues: “*History of science teaches us that scientific endeavour has often in the past wasted effort in fields with absolutely no yield of true scientific information...Of course, investigators working in any field are likely to resist accepting that the whole field in which they have spent their careers is a ‘null field’*” (PloS Medicine 2005:2:8:e124).

Clear-eyed analysis of the results of the PACE Trial as published in The Lancet suggests a classic case of authors unwilling to accept that they have indeed spent their careers in a “*null field*” in relation to their efforts to designate ME/CFS as a behavioural disorder. Unfortunately, the many deficiencies in the published article appear to have evaded the rigours of The Lancet’s peer review process. Furthermore,

the glowing commentary published in The Lancet (by authors with a published record of bias) is quite untenable.

Other competing interests and biases have been identified, all of which appear to occur in the PACE Trial, including population choice bias; severity of illness bias (patients with a mild form of an illness may not respond in the same way as those with a more severe form); comparison choice; outcome choice bias; withdrawal bias; bias introduced by inappropriate handling of withdrawals, drop-outs and protocol violations; missing data bias; publication bias; moral bias; values bias; printed word bias (when a study is overrated because of undue confidence); prominent author bias (when the results of studies published by prominent authors are overrated, including esteemed author bias and esteemed professor bias); multicentre collaborative trials (when the results are overrated); vested interest bias; cherished belief bias and empiricism bias (Random Controlled Trials. A Jadad & M Elkin; Oxford, Blackwell 2007; first published in 1998).

#### GIJS BLEIJENBERG AND HANS KNOOP

The fast tracked publication of the PACE Trial results was accompanied by a commentary titled “*Chronic fatigue syndrome: where to PACE from here?*” written by Gijs Bleijenberg and Hans Knoop. No actual or potential conflicts of interest were published in respect of these authors, which was a serious omission.

A cursory glance at the references cited illustrates that these authors have a particular track record in this field.

Illustrations of relevant extracts are:

“*Few patients receiving cognitive behaviour therapy or graded exercise therapy in the PACE trial had serious adverse reactions and no more than those receiving adaptive pacing therapy or standard medical care, which for cognitive behavioural therapy has already been shown*” (Possible detrimental effects of cognitive behaviour therapy for chronic fatigue syndrome. Heins M, **Knoop H**, Stulemeijer M, Prins JB, Van der Meer JWM, **Bleijenberg G**. Psychother Psychosom 2010;79:249-256).

“*Graded exercise therapy and cognitive behaviour therapy might assume that recovery from chronic fatigue syndrome is possible, but have patients recovered after treatment? The answer depends on one’s definition of recovery*” (Is a full recovery possible after cognitive behavioural therapy for chronic fatigue syndrome? **Knoop H**, **Bleijenberg G**, Gielissen MFM, van der Meer JWM, **White PD**. Psychother Psychosom 2007;76:171-176).

“*Wiborg and colleagues have shown that the effect of cognitive behaviour therapy on fatigue in chronic fatigue syndrome is not mediated by a persistent increase in physical activity*” (How does cognitive behaviour therapy reduce fatigue in patients with chronic fatigue syndrome? The role of physical activity. Wiborg JF, **Knoop H**, Stulemeijer M, Prins JB, **Bleijenberg G**. Psychol Med 2010; **40**: 1281–87).

***“We noted that a decrease in focus on fatigue mediated the effect of cognitive behaviour therapy on fatigue and impairments in patients with the syndrome”*** (Does a decrease in avoidance behavior and focusing on fatigue mediate the effect of cognitive behaviour therapy for chronic fatigue syndrome? Wiborg JF, **Knoop H**, Prins JB, **Bleijenberg G**. J Psychosom Res 2011; published online Feb 12.

Consideration of the references in the PACE Trial article itself is similarly revealing. The very first sentence of the article, describing CFS, is linked to an article of which Bleijenberg was an author: ***“Chronic fatigue syndrome is characterised by chronic disabling fatigue in the absence of an alternative diagnosis”*** (Chronic fatigue syndrome. Prins JB, van der Meer JW, **Bleijenberg G**. Lancet 2006;367:346-355).

Perhaps most remarkably of all, the description of the CBT approach used in the PACE Trial states: ***“Therapy manuals were based on manuals used in previous trials”*** and cites three publications, including one by Bleijenberg (Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomized controlled trial. Prins JB, **Bleijenberg G**, Bazelmans E, et al. Lancet 2001; **357**: 841–47).

**Gijs Bleijenberg was one of the authors of a manual on which the PACE Trial CBT manual was based.**

Furthermore, the (very inadequate) consideration of safety in the PACE Trial publication concludes with:

***“Consequently, if these treatments are delivered as described, by similarly qualified and trained clinicians, patients need not be concerned about safety”***, referencing this to a Knoop and Bleijenberg paper which was also self-referenced in their commentary article (Possible detrimental effects of cognitive behaviour therapy for chronic fatigue syndrome. Heins MJ, **Knoop H**, Prins JB, Stulemeijer M, van der Meer JWM, **Bleijenberg G**. Psychother Psychosom 2010; **79**: 249–56.

Additionally, The Lancet reviewers/editorial staff should have readily been able to discover for themselves that Bleijenberg was among the authors of the CBT cost effectiveness analysis which played a key role in the considerations of the National Institute for Health and Clinical Excellence’s Guideline Development Group on “CFS/ME”. The relevant publication is: Cost effectiveness of cognitive behaviour therapy for patients with chronic fatigue syndrome. Severens JL, Prins JB, van der Wilt GJ, van der Meer JW, **Bleijenberg G**. Q Med 2004; 97(3):153-161.

Not only does this show a close connection with the PACE Trial and PACE Trial Investigators, but it also demonstrates that Bleijenberg and Knoop are closely associated with the same psychosomatic/functional perspective on “CFS”, which makes them party to the many shortcomings and deficiencies of this illegitimate approach, as demonstrated in other sections of this report.

#### 4. THE PIs WERE NOT STUDYING CLASSIC ME/CFS

There is some confusion as to which disorder or disorders the PIs were studying. This is a matter of utmost importance to clarify, since interventions that may benefit one patient group within the broad spectrum of “CFS” are likely to cause iatrogenic harm to others.

The PACE Trial Protocol gives the title of the trial as “*A randomised controlled trial...for patients with the chronic fatigue syndrome/myalgic encephalomyelitis or encephalopathy*”.

In the Glossary to the Full Protocol, White et al state that CFS/ME is the official term for the illness as described in the “*Working Group Report to the Chief Medical Officer (2002) and the MRC RAG Report (2003)*”.

In the Patient Clinic Leaflet, White et al state: “*This illness is also known as post-viral fatigue syndrome, myalgic encephalomyelitis (ME) and myalgic encephalopathy (ME). Medical authorities are not certain that CFS is exactly the same illness as ME...but we will be calling this illness CFS/ME*”.

However, in The Lancet article, what White et al referred to in the Full Protocol as the “official term” for the disorder (“CFS/ME”) is not used at all, only the term “*chronic fatigue syndrome*” and, as noted above, the title of The Lancet article omits all mention of the term “ME”.

It is thus not readily discernible whether what White et al alleged they would be studying is the same disorder (or more accurately, disorders) that they did study.

The authors stated in the Protocol that they would be studying chronic fatigue syndrome, and that some are of the view that this is the same as “*myalgic encephalomyelitis or encephalopathy (ME)*”, whilst others do not share that view. They ally themselves with the former view but in the published Lancet article they do not ally themselves with one perspective or the other.

In The Lancet article, the authors state that: “*CBT was done on the basis of the fear avoidance theory of chronic fatigue syndrome. This theory regards chronic fatigue syndrome as being reversible and that cognitive responses (fear of engaging in activity) and behavioural responses (avoidance of activity) are linked and interact with physiological processes to perpetuate fatigue. The aim of treatment was to change the behavioural and cognitive factors assumed to be responsible for perpetuation of the participant’s symptoms and disability*” and that GET “*was done on the basis of deconditioning and exercise intolerance theories of chronic fatigue syndrome. These theories assume that the syndrome is perpetuated by reversible physiological changes of deconditioning and avoidance of activity. These changes result in the deconditioning being maintained and an increased perception of effort, leading to further inactivity*”.

This statement clearly shows that the PACE Trial was predicated on a false premise, as by no credible means can ME/CFS be categorised as a functional disorder, yet this

is exactly what the PIs did without challenge by the MRC or by any ethics committee (including the MRC's Data Monitoring and Ethics Committee).

This may be seen as collusion in what many international commentators have deemed a fraudulent study that was designed and carried out for non-clinical purposes, namely to "eradicate" ME (see Appendix 1) and to re-categorise "CFS" as a functional disorder, thus removing it from insurance cover and from higher rates of State benefits.

Illustrations of papers that disprove the "deconditioning" theory in ME/CFS include (i) Scroop GC et al; *Med J Aust* 2004;181:578-580; (ii) Schmaling KB et al; *J Psychosom Res* 2005;58(4):375-381; (iii) Newton JL et al; *Q J Med* 2007;100:519-526.

In plain terms, "CFS/ME" as created by the Wessely School is very different from ME/CFS. The former is believed by them to be a behavioural disorder, whilst the latter is known (and scientifically proven) to be a biomedical disorder.

The Investigators ignored the extensive biomedical research literature and mis-portrayed ME/CFS as a dysfunctional belief instead of a serious multi-system chronic neuroimmune disease. Even though they acknowledge they do not know what causes "CFS/ME", in the CBT and GET arms of the trial the PIs assumed (and instructed the trial therapists) that participants had no physical disease but did not inform participants of this and portrayed their own assumptions as established facts, which is misleading and scientifically untenable. That meant that patients were unable to give fully informed consent as required for a clinical trial.

Illustrations of the extensive and significant biomedical evidence that the PIs chose to disregard can be accessed at: <http://www.mereseearch.org.uk/information/researchdbase/index.html> and at <http://www.meactionuk.org.uk/magical-medicine.htm> Section 2, pages 98 to 214.

There are known biomarkers for ME/CFS. Recent scientific research has revealed that from a comprehensive list of 30,000 peptides, 738 proteins were found only in (ME)CFS subjects' cerebrospinal fluid (ie. not in normal controls or other disorders), which the authors contend adds to the ever-increasing number of biomarkers for ME/CFS (Schutzer SE et al; *PloS ONE* 6(2): e17287. doi:10.1371.journal.pone.0017287).

Many other such biomarkers exist for the identification of ME/CFS, for example:

- "Biomarkers in chronic fatigue syndrome: evaluation of natural killer function and dipeptidyl peptidase IV/CD26" (Fletcher MA et al; *PloS ONE*: 2010 May 25; 5(5): e10817); the authors concluded: "*Abnormalities in DPPIV/CD26 and in NK cell function have particular relevance to the possible role of infection in the initiation and/or the persistence of CFS*".
- "Plasma neuropeptide Y: a marker for symptoms severity in chronic fatigue syndrome" (Fletcher MA et al; *Behav Brain Funct* 2010: Dec 29:6:76); the authors stated: "*CFS is a complex, multi-symptom illness with a multi-system*

*pathogenesis involving alterations in the nervous, endocrine and immune systems. Abnormalities in the stress responses have been identified as potential triggers or mediators of CFS symptoms....This study is the first in the CFS literature to report that plasma NPY is elevated compared to healthy controls...(which) suggests that this peptide should be considered as a biomarker to distinguish subsets of CFS”.*

- “Severity of symptom flare after moderate exercise is linked to cytokine activity in chronic fatigue syndrome” (White AT, Light AR et al; Psychophysiology 2010 Jul 1; 47(4):615-624. Epub 2010 Mar 4).
- “Moderate exercise increases expression for sensory, adrenergic, and immune genes in chronic fatigue syndrome patients but not in normal subjects” (Light AR et al; J Pain 2009: Oct 10 (10):1099-1112. Epub 2009 Jul 31); the authors demonstrated that after moderate exercise, CFS subjects showed enhanced gene expression for receptors detecting muscle metabolites and for SNS and IS, which correlated with symptoms, suggesting these are objective biomarkers for CFS.
- “Abnormal impedance cardiography predicts symptom severity in chronic fatigue syndrome” (Peckerman A et al; Am J Med Sci 2003:Aug; 326(2):55-60); the authors showed that patients with severe CFS had significantly lower stroke volume and cardiac output than controls.

Virtually all the biomedical evidence was extant at the time of the PACE Trial but was comprehensively ignored by the PIs because, had it been taken on board, the various ethics committees would not have been able to approve the PACE Trial in the PIs’ chosen design that was intended to produce the desired outcome.

### The entry criteria

PACE Trial participants were recruited according to the Oxford criteria for chronic fatigue (JRSM 1991:84:118-121) but what the Wessely School refer to as CFS/ME is not what international experts regard as ME/CFS.

The Oxford criteria have been roundly criticised by international investigators and by patient groups for their lack of specificity and because they expressly exclude those with **“proven organic brain disease”** (which ME/CFS has been internationally shown to be in numerous brain imaging studies) whilst expressly including those with affective disorders such as anxiety and depression.

The choice of the Oxford criteria is noteworthy, given that one of the Principal Investigators himself (Professor Sharpe) stated in 1997 that the Oxford criteria **“have been superseded by international consensus”** (Chronic fatigue syndrome and occupational health. A Mountstephen and M Sharpe. Occup Med 1997:47:4:217-227). It is highly unusual to use criteria in a clinical trial that have been superseded.

However, contrary to accepted scientific practice, those superseded criteria were deliberately chosen in order to enhance applicability to as large a number of “fatigued” people as possible and thus to enhance recruitment to the trial.

The Trial Identifier states at section 3.6: *“Subjects will be required to meet operationalised Oxford criteria for CFS. This means six months or more of medically unexplained, severe, disabling fatigue affecting physical and mental functions. We chose these broad criteria in order to enhance generalisability and recruitment”*.

Deliberately to broaden entry criteria for a clinical trial so that they include patients who do not have the disorder in question contravenes elementary rules of scientific procedure.

One of the authors of the Oxford criteria, psychiatrist Professor Anthony David, clarified the issue of whether or not the Oxford criteria exclude people with neurological disorders:

*“British investigators have put forward an alternative, less strict, operational definition which is essentially chronic (6 months or more) ...fatigue in the absence of neurological signs, (with) psychiatric symptoms...as common associated features”* (A.S. David; BMB 1991:47:4:966-988).

That is not a definition of ME/CFS.

As Dr Melvin Ramsay, the “Father” of ME, pointed out many times (in published articles, in the ME Association magazine and in presentations) there are always neurological signs in ME/CFS.

Furthermore, the Chief Principal Investigator himself (Peter White) has previously acknowledged that the Oxford criteria *“allow co-morbid mood disorders”* and warned that his own data *“suggest that the Oxford criteria should be used with caution”* when attempting to distinguish between ME/CFS and mood disorders (Lancet 2001:358:9297:1946-1953).

Six years earlier, White stated: *“...the complaint of post-exertional physical fatigue may help to differentiate post-viral fatigue states from psychiatric disorders...This study provides evidence that previous definitions have been over-inclusive, and that the post-viral fatigue syndrome is probably not a misclassified psychiatric disorder...This is the first clinical evidence to suggest that a postviral fatigue syndrome is a discrete, valid and reliable condition. This supports the differentiation found with endocrine measures in the chronic fatigue syndrome”* (Psychological Medicine 1995:25(5):917-924).

Professor White is also on record in 1995 stating: *“The Oxford criteria are more widely defined...(and) allow the inclusion of affective illnesses....There are marked discrepancies between the empirical syndrome and descriptions of myalgic encephalomyelitis....These descriptions included physical symptoms which are not found in our syndrome, such as ... dysequilibrium, hot flushes and”*

**myalgia...These discrepancies may be because myalgic encephalomyelitis is a different illness**” (Psychol Med 1995:25(5):907-916).

Thus it is clear that the Chief Principal Investigator was fully aware of key differences between ME/CFS and other fatigue states, yet he chose to amalgamate them into one heterogeneous cohort for the PACE Trial.

Because ME/CFS is a classified neurological disorder and the Oxford criteria exclude those with a neurological disorder, many people raised concerns with the MRC about the validity of the PACE Trial, but on 16<sup>th</sup> June 2005, Dr Sarah Perkins, Programme Manager, MRC Neurosciences and Mental Health Board, wrote about the Oxford criteria: ***“Their use will ensure that the results of the trials will be applicable to the widest range of people who received a diagnosis of CFS/ME. The exclusion criterion of ‘proven organic brain disease’ will be used to exclude neurological conditions....It will not be used to exclude patients with a diagnosis of ME”.***

It is scientifically invalid for the Wessely School to assert that the Oxford criteria do not exclude those with ME (a WHO classified neurological disorder) on the basis that the Wessely School do not accept that ME is a neurological disorder.

The PACE Trial Investigators have intentionally mixed at least three taxonomically different disorders in the trial cohort -- those who the Investigators claim to suffer from ME/CFS (ICD-10 G93.3), even though the entry criteria exclude such patients; those with fibromyalgia (ICD-10 M79.0) and those with a mental/behavioural disorder (ICD-10 F48.0).

As noted above, the PIs chose to include patients with fibromyalgia in the PACE Trial because (despite the significant literature that disproves their out-dated belief), they believe it, like ME/CFS, to be a functional disorder (Functional somatic syndromes: one or many? S Wessely, M Sharpe et al. Lancet 1999:354:936-939).

On 12<sup>th</sup> May 2004, Minister of State Dr Stephen Ladyman MP confirmed at the All Party Parliamentary Group on FM that doctors were being offered financial inducements to persuade those with fibromyalgia (ie. people who did not have ME/CFS) to enter the PACE Trial.

Not only is fibromyalgia classified as a distinct disorder in ICD-10, it is known to be genetically different from ME/CFS (Keynote Lecture by Dr Estibaliz Olano: Genetic Profiles in Severe Forms of Fibromyalgia and Chronic Fatigue Syndrome; MERUK International Research Conference, Heriot Watt University, Edinburgh, 25<sup>th</sup> May 2007). The study revealed ***“two very defined differences (with) a very clear discrimination between FM and (ME)CFS, with 95.4% specificity”.*** Dr Olano said: ***“If you look at the genes that were involved with the diseases, (ME)CFS has an important autoimmune background to it – we had cytokines, among them IL-10, (and) many polymorphisms in the genes related to immune and inflammation markers were different in (ME)CFS people but not in FM people. In (ME)CFS, the genetic background has to do with immune genes and neurological genes (and) in FM it was more neurological genes which were involved, so there are two different diseases with two different genetic backgrounds”.***

There are many biochemical differences between ME/CFS and FM, for example:

- levels of somatomedin C are lower in FM patients but are higher in ME/CFS patients (J psychiat Res 1997:31:1:91-96)
- levels of Substance P are elevated in patients with ME/CFS but not in patients with FM (Pain 1998:78:2:153-155)
- patients with FM are not acetylcholine sensitive (Rheumatology 2001:40:1097-1101) but patients with ME/CFS are acetylcholine sensitive (Prostaglandins, Leukotrienes and Essential Fatty Acids 2004:70:403-407)
- endothelin-1 is raised in fibromyalgia (Rheumatology 2003:42:493-494) but is normal in ME/CFS (Rheumatology 2004:43:252-253).

FM has a distinct biological profile that is different from ME/CFS, so it is unclear how the intentional inclusion of different disorders in an MRC trial evaded detection by the allegedly rigorous monitoring process.

As mentioned above, on 14<sup>th</sup> July 2006 Professor White sought approval from the West Midlands MREC to advertise his PACE Trial to doctors and to ask them to refer anyone “*whose main complaint is fatigue (or a synonym)*” to enter the trial.

The MRC was asked how the deliberate inclusion of anyone who was fatigued (ie. tired) and of people with taxonomically different disorders could not result in skewed and meaningless conclusions when, from the outset, patients being entered into the PACE trial were not clearly defined, a question that elicited no response.

The Oxford criteria have never been adopted internationally. There is no consensus about them; they are used only in Britain and only by the Wessely School. They lack diagnostic specificity, have been shown to have no predictive validity, and to select a widely heterogeneous patient population with idiopathic fatigue.

As long as researchers can select whichever definition of a disorder they choose, they will inevitably select the one that suits their purpose ---- in this case, their own criteria that were designed to support their own beliefs.

The Oxford entry criteria for the PACE Trial do not take into account the severity of the symptoms. No severely affected people were involved in the trial so it is inappropriate for White et al to generalise their results and to conclude that “*CBT and GET can safely be added to SMC to moderately improve outcomes for chronic fatigue syndrome*” when the PACE cohort was not a representative sample of people with ME/CFS.

Indeed, it is unclear if anyone with classic ME/CFS was included in the PACE Trial because of the laxity of the entry criteria.

Whilst the Oxford criteria were used for the entry criteria, the “London Criteria” were to be used for “secondary analysis”, but the “London Criteria” do not even exist.

By letter dated 16<sup>th</sup> June 2005, Dr Sarah Perkins, Programme Manager, MRC Neurosciences and Mental Health Board, wrote about the “London Criteria” for ME: ***“I should emphasise that the London criteria will not be used as an inclusion criteria but will be used as predictors of response to treatment”.***

It is a straightforward fact that if those with a classified neurological disorder are excluded from the outset by correct application of the Oxford entry criteria, no amount of “secondary analysis” will reveal those with a classified neurological disorder.

The issue of case definition to be used by the MRC for “secondary analysis” is of cardinal importance, yet the provenance of the “London Criteria” has not been established.

The “London Criteria” have never been published in any medical journal and are not on PubMed so are not available for scrutiny or comparison. There is no methods paper which specifically describes them as a “case definition”; they have never been approved nor have they even been finally defined (there are various versions); despite numerous claims on the internet by one of the alleged authors (the same person both claimed and denied authorship), it remains uncertain who the authors are or which of the numerous proposed versions is to be preferred.

This means that Professor White was able to (and did) create his own version of the “London Criteria” as evidenced on page 188 of the Full Protocol. In fact, Professor White amended the Protocol and he substituted his own version of the “London Criteria” for the Ramsay definition (Professor White’s “version 2” is dated 26.11.2004).

The original intention of the PIs was to use the Ramsay definition of ME and this was date-stamped by the MREC as received on 21<sup>st</sup> March 2003 (<http://www.meactionuk.org.uk/magical-medicine.htm>, page 417).

The Ramsay definition of ME as approved by the MREC required the following: fluctuation of symptoms from day to day or within the day; headaches; giddiness; muscle pain; muscle cramps; muscle twitchings; muscle tenderness; muscle weakness; pins and needles; frequency of passing water; blurred vision; double vision; increased sensitivity of hearing; increased sensitivity to noise; feeling generally awful, and muscle weakness after exercise.

Whilst the Ramsay definition does exist (Postgrad Med J 1990:66:526-530), the “London Criteria” do not in fact exist and the reference cited in the Lancet paper is to the 2004 Westcare Report, which simply said that they were “proposed” criteria.

Professor White’s own version of the “London Criteria” specifically states on page 188 of the Full Protocol that neurological disturbances ***“are not necessary to make the diagnosis”*** and they further state that: ***“the usual precipitation by ‘physical or mental exercise’ should be recorded but is not necessary to meet criteria”.***

**Put another way, Professor White’s “London Criteria” do not require the cardinal feature of ME to be present in his subgroup of patients in a trial that purported to be studying “CFS/ME”.**

Notwithstanding the clear statement in the Full Protocol that postexertional malaise is not necessary to meet the London Criteria, the text of the Lancet article states that participants were also assessed by *“the London criteria for myalgic encephalomyelitis (version 2) requiring postexertional fatigue”* when, according to Professor White’s own “London Criteria”, this was not the case.

This is a significant discrepancy that requires explanation by Professor White, since two such divergent criteria cannot both have been used in the PACE Trial.

**This raises the question as to what disorder was being studied in this subgroup, because the clear distinction between Ramsay-defined ME and somatisation disorder has been significantly lessened by the PIs, which accounts for the remarkable similarity of results between the “London” subgroup and the full cohort.**

This is an issue for Professor White to address, because he needs to clarify whether or not he adhered to his own Protocol as required.

Following publication of the PACE Trial results in The Lancet, an article by David Tuller appeared in the New York Times on 4<sup>th</sup> March 2011 which said:

*“Now a new study of chronic fatigue syndrome has highlighted how competing case definitions can lead to an epidemiologic ‘Rashomon’ – what you see depends on who’s doing the looking – and has stoked a fierce debate among researchers and patient advocates on both sides of the Atlantic....The British scientists who conducted the research identified study participants based largely on a single symptom: disabling and unexplained fatigue....whether a definition is broadly or narrowly drawn can profoundly affect the statistics vital for public health planning....A 2003 case definition from Canada elevates postexertional malaise to a central role in the illness and requires a range of neurological, cognitive, endocrine (and) immunological symptoms....”.*

Professor Leonard Jason, a US internationally-renowned expert on the disorder, has once again emphasised the importance of the cardinal feature of post-exertional malaise in ME/CFS; he has shown that over time, (ME)CFS patients remain ill with relative stability of critical measures of disability:

*“However, among all the variables in this study, only for post-exertional malaise did the (ME)CFS group significantly differ from the three other conditions. This reaffirms the importance of this being a cardinal and critical symptom for (ME)CFS....the symptom post-exertional malaise appears to be unique in differentiating (ME)CFS from other groups, and this symptom is required for a diagnosis of ME/CFS based on the Canadian ME/CFS criteria (Carruthers et al, 2003). However, post-exertional malaise is not required for the Fukuda et al (1994) case definition”* (A Natural History Study of Chronic Fatigue Syndrome. Leonard A Jason et al; Rehabilitation Psychology 2011; in press).

Given that post-exertional fatiguability with malaise is the cardinal feature of ME/CFS and that without it, the disorder cannot be diagnosed, it defies credibility that the Chief Principal Investigator, Professor Peter White, did not require the cardinal feature of ME/CFS to be present in his cohort of patients in a trial that purported to be studying it.

It is notable that in The Lancet article, White states: “*Several diagnostic criteria exist for chronic fatigue syndrome and myalgic encephalomyelitis*”. This statement is selectively referenced only to those criteria that are used in the PACE Trial itself. In other words, White mentions only the ones of which he personally approves and, because he disapproves of them, he omits even to mention the acclaimed Canadian Criteria which have impressive credentials (Carruthers B et al; Myalgic Encephalomyelitis / Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols (JCFS 2003:11(1):7-115).

ME/CFS has been defined in the Canadian Guidelines (2003), which have been adopted internationally and are the best aid to the diagnosis of ME/CFS but which the Chief Investigator Peter White insists should not be used in the UK because they unambiguously do not accept his own beliefs, for example, the Canadian criteria state:

*‘The question arises whether a formal CBT or GET programme adds anything to what is available in the ordinary medical setting. A well-informed physician empowers the patients by respecting their experiences, counsels the patients in coping strategies, and helps them achieve optimal exercise and activity levels within their limits in a common-sense, non-ideological manner, which is not tied to deadlines or other hidden agenda’.*

The Canadian criteria are “*a systematic clinical working case definition that encourages a diagnosis based on characteristic patterns of symptoms clusters which reflect specific areas of pathogenesis*” and are based on the authors’ collective extensive experience of diagnosing and/or treating more than twenty thousand ME/CFS patients. The authors state about the Canadian guidelines: “*We believe this will sharpen the distinction between ME/CFS and other...conditions that may be confused with it in the absence of a definitive laboratory test for ME/CFS....The panel felt there was a need for the criteria to encompass more symptoms in order to reflect ME/CFS as a distinct entity....As fatigue is an integral part of many illnesses, the panel concurred that more of the prominent symptoms should be compulsory*”.

In a broadcast on the BBC Radio 4 “Today” programme transmitted on 5<sup>th</sup> November 2007, Professor White was very clear about his dislike of the Canadian criteria.

When asked by the interviewer about the Canadian Guidelines, he said he did not like them:

*“The problem is, and the reason why I don’t use them, is they’re very complicated to use and would require me to actually do tests on my patients that I don’t think I ethically should be doing on my patients, and I don’t find them useful, and if Guidelines aren’t useful, then we don’t use them”.*

The interviewer said: *“You mentioned tests that you don’t think it’s right for you to do, such as ...?”*, to which White responded: *“Such as the tilt table test – I would have to exclude a condition called POTS (where the blood pressure falls on standing up). I don’t think that’s justified”*.

The interviewer asked: *“So you think they’re unethical because they’re too demanding?”*, to which White’s immediate answer was: *“Yes”*.

When transmission ended, Dr William Weir (another interviewee and a consultant physician who does not subscribe to the Wessely School’s beliefs about ME/CFS) turned to Professor White and said (words to the effect of): *“Peter, I’m glad to hear you state that ME is not a psychological disorder. This must mean that things have moved on from illness beliefs”*, whereupon Professor White’s immediate response was (verbatim): *“Oh no, it IS an abnormal illness belief”* ([http://www.meactionuk.org.uk/Whiter\\_than\\_white.htm](http://www.meactionuk.org.uk/Whiter_than_white.htm)).

**Since the general body of knowledge known about by other clinicians and researchers working in the field of ME/CFS is now so great, the question repeatedly asked is: at what point will that body of scientific knowledge be so great that it will be considered serious professional misconduct to ignore it and to continue to deceive patients by pretending that it does not exist?**

The Full Canadian Guidelines can be accessed at <http://www.cfids-cab.org/MESA/ccpccd.pdf> and a Summary can be accessed at <http://www.cfids-cab.org/MESA/ccpc.html>

The disregard for the evidence-base about the nature of this disorder is manifestly apparent from the authors’ descriptions of their rationale for CBT and GET as presented in Panel 1 of the published PACE Trial article. The putative “fear avoidance” and “deconditioning” theories are at the very least severely undermined by a comprehensive appraisal of the biomedical science.

**Such an appraisal strongly suggests that the trial was based on a myth that has been allowed to masquerade as science, namely that ME/CFS is not a complex multi-system inflammatory neuroimmune disorder but, by calling it “CFS/ME”, a somatoform disorder that can be reversed by the PIs’ own version of psychotherapy.**

Eager to defend his own Oxford criteria, together with the other two PIs (Professor Sharpe and Chalder), on 14<sup>th</sup> March 2011 Professor White replied to the letter from David Tuller in the New York Times mentioned above; attempting to justify the use of the overly-broad Oxford criteria, White stated: *“...that is the definition of the syndrome used in Britain. But we also assessed trial participants to see if they met two other definitions of the illness that are favoured by some scientists. We found that both cognitive behaviour therapy and graded exercise therapy, when added to specialist medical care, were most effective not only in the whole sample but also in the participants who met these alternative criteria”*.

That statement is misleading for two reasons: (i) not only did White not use the most widely-used CDC international criteria of 1994 (the Fukuda et al criteria) as indicated in the Trial Identifier -- he substituted the 2003 Reeves et al criteria but referred to them as “*international criteria for chronic fatigue syndrome*”, when to do so was confusing and (ii) he created his own version of the unpublished “London Criteria”, which means that the clear distinction between ME/CFS and somatoform disorders was thereby lessened.

White et al’s reply to Tuller continued: “*So to Mr. Tuller’s question ‘Does the evidence from that study prove that these strategies would help patients identified as having chronic fatigue syndrome through very different criteria?’ the answer is ‘Yes, it does.’ Patients and their doctors now have robust evidence that there are two safe treatments that can improve both symptoms and quality of life, however the illness is defined*”.

The statistical analyses contained in this complaint clearly show that White et al are incorrect in their assertions, but this collective outburst from the three PIs showed the world that science, medicine and the welfare of sick people apparently do not concern Professors White, Sharpe and Chalder.

David Tuller’s response to White et al was succinct: “*The article asked whether the findings among a population defined by one set of criteria would apply to populations defined by ‘very different criteria’....The gold standard for making comparisons across groups of patients identified by three varying case definitions would be a study with three completely separate cohorts, not one large sample with two embedded subgroups*”.

It is disturbing that the PIs persist in disregarding the evidence that contradicts their own beliefs and that they continue to regard ME/CFS as reversible deconditioning caused by aberrant illness beliefs.

## **5. FAILURE TO COMPLY WITH PROFESSIONAL ETHICAL GUIDANCE AND CODES OF PRACTICE**

In the PACE Trial Protocol, the authors state their intention to comply with certain codes of practice:

*“The trial will be conducted in compliance with the Declaration of Helsinki, the trial protocol, MRC Good Clinical Practice (GCP) guidance, the Data Protection Act (1998), the Multi-centre Research Ethics Committee (MREC) and Local Research Ethics Committees (LREC) approvals and other regulatory requirements, as appropriate. The final trial publication will include all items recommended under CONSORT (Consolidated Standards of Reporting Trials)”.*

Although not mentioned, the provisions of the General Medical Council Guidance Good Practice in Research and Consent to Research would also appear to apply, as would to the provisions of the Department of Health Research Governance Framework for Health and Social Care, Second Edition, 2005; 2:3:1 .

There appear to have been some notable failures in this regard.

### Breaches of the Declaration of Helsinki

It appears that the PACE Trial did not conform to the Declaration of Helsinki in full, for example:

- participants and others have asserted that coercion was used (breaching A5, A8, B20 and B22): it is understood that the policy at the now-closed Fatigue Clinic at the Royal Free Hospital was that patients who were asked but declined to enter the PACE Trial were to be discharged from the Clinic and would have no further access to a Clinic doctor for medical advice (access which, apart from symptomatic medical care, they might need in order to support a claim for State benefits, as a GP cannot endorse an application for Disability Living Allowance). Having to choose between the option of an inappropriate intervention or no intervention plus no further access to a clinic doctor is not true consent. **If Professor White (who was in overall charge of the RFH Fatigue clinic) was recruiting patients attending the Royal Free Fatigue Service Clinic to the PACE Trial on the basis that non-compliers would be discharged from the Clinic raises the possibility that he was recruiting only CBT/GET-compliant patients to his MRC trial, which would decrease the number of trial drop-outs at a stroke, and this would be to his advantage** (see [http://www.meactionuk.org.uk/COERCION\\_AS\\_Cure.htm](http://www.meactionuk.org.uk/COERCION_AS_Cure.htm)); furthermore, as noted above, a Minister of State confirmed that GPs were offered financial inducements to procure participants for the trial, and those GPs may have brought undue pressure on patients to enter the trial, which in turn may have compromised their own relationship with patients
- the PIs' hypotheses were asserted as working perspectives without assessment against relevant biomedical evidence, which would have undermined their hypotheses entirely (breaching B11)
- the Investigators' conflicts of interest were initially denied; participants were not fully informed of the Investigators' institutional affiliations; the anticipated benefits of the interventions were greatly overplayed to those in the CBT and GET groups but not in the APT or SMC groups (breaching B13 and B22)
- there are well-documented adverse consequences of aerobic exercise for patients with ME/CFS; these include the effects of increased oxidative stress; the effects on cardiac output and function, and the effects of exercise on the already disrupted immune system (breaching B17). The Chief PI's own research shows that that the pro-inflammatory cytokine TNF $\alpha$  remains elevated three days after exercise in "CFS/ME" patients (JCFS 2004:12(2):51-66): *"The pro-inflammatory TNF $\alpha$  is known to be a cause of acute sickness behaviour, characterized by reduced activity related to 'weakness, malaise,*

*listlessness and inability to concentrate’, symptoms also notable in CFS”*  
(JCFS 2004:12 (2):51-66)

- participants’ confidential data was not kept securely and was stolen (breaching B21) (<http://www.meactionyk.org.uk/magical-medicine.htm> page 256)
- the Investigators ignored the scientific literature that differentiates ME/CFS from “chronic fatigue” (breaching B11)
- as noted above, the Investigators already knew that *“These interventions are not the answer to CFS”* (Editorial: Simon Wessely; JAMA 19<sup>th</sup> September 2001:286:11) and that *“many CFS patients, in specialised treatment centres and the wider world, do not benefit from these interventions”* (Huibers and Wessely; Psychological Medicine 2006:36:(7):895-900) (breaching B19)
- participants were not informed of the potential risks inherent in the trial , in particular they were not informed of the nature, degree, or duration of the discomfort or relapse they might reasonably be expected to experience through participating in aerobic exercise in the PACE Trial; furthermore coercion was used to prevent participants from withdrawing from the trial (breaching B22) (<http://www.meactionuk.org.uk/magical-medicine.htm> pages 236-237).

#### Breaches of the General Medical Council Research Guidance

It appears that the PIs likewise failed to observe relevant principles of good research required by the GMC “Good practice in research and Consent to research” as set out at [http://www.gmc-uk.org/static/documents/content/Research\\_guidance\\_FINAL.pdf](http://www.gmc-uk.org/static/documents/content/Research_guidance_FINAL.pdf).

For example, the following paragraphs apply:

- paragraph 5: *“To protect participants and maintain public confidence in research, it is important that all research is conducted...with honesty and integrity”*
- paragraph 8: *“You must make sure that the safety, dignity and wellbeing of participants takes precedence over the development of treatments”*
- paragraph 9: *“You must be satisfied that the anticipated benefits to participants outweigh the foreseeable risks”*
- paragraph 13: *“You must keep your knowledge and skills up to date”*
- paragraph 17: *“You should make sure that any necessary safeguards are in place to protect anybody who may be vulnerable to pressure to take part in research”*
- paragraph 21: *“You must conduct research honestly”*

- paragraph 22: *“You must be open and honest with participants....You must answer questions honestly and as fully as possible”*
- paragraph 24: *“You must report research results accurately, objectively, promptly, and in a way that can be clearly understood. You must make sure that research reports ...do not contain false or misleading data”*
- paragraph 27: *“You must not allow your judgment about a research project to be influenced, or seen to be influenced, at any stage, by financial, personal, political or other external interests”*
- paragraph 29: *“You must make sure that...you respect their right to decline to take part in research and to withdraw from the research project at any time”*
- paragraph 31: *“You must...make sure that any data collected as part of a research project are stored securely”*.

#### Breaches of the CONSORT Statement

The CONSORT statement ([www.bmj.com/content/340/bmj.c869.full](http://www.bmj.com/content/340/bmj.c869.full)) says: *“Trial reports need to be clear, complete, and transparent”*; as detailed below, The Lancet article fails these criteria. Regarding the recording of sessions during the trial, both the CBT (page 26) and GET (page 29) Therapists’ Manuals advise therapists that *“If participants are unclear of the reasons, you can remind them that you are doing this for the purposes of supervision, assessment of competence, assessment of therapy differences and other research purposes”*, but no explanation was provided regarding *“other research purposes”*. Could it have been for the *“research purposes”* of the DWP? What did participants understand these *“other research purposes”* to be? Not to inform participants of the precise nature of these *“other research purposes”* does not accord with the research requirement for transparency.

Furthermore, Professor White has demonstrably failed to adhere to CONSORT: for him not to have reported the number of participants who recovered was a significant omission on his part, especially as he has claimed that full recovery is possible after CBT/GET (Psychother Psychosom 2007;76(3):171-176) and as selected participants were specifically informed that they could recover with those particular interventions.

In the interests of openness and transparency in research, White also failed to comment on a major and far-reaching issue, namely, that the PACE Trial results show that his favoured “cognitive behavioural” model of ME/CFS has been comprehensively demolished, as the PACE Trial statistics clearly show (see below).

#### Examples of unethical dealings with participants

(i) Misinformatting participants about the nature of the disorder

The Wessely School insist that the distressing organic symptoms seen in ME/CFS are not the result of any pathological process but are merely hypervigilance to normal bodily sensations (The Cognitive Behavioural Management of the Post-viral Fatigue Syndrome; S Wessely, T Chalder et al; In: Post-Viral Fatigue Syndrome, ed. Rachel Jenkins and James Mowbray, John Wiley & Sons, 1991, page 311) which White believes are *“enhanced interoception (the perception of visceral phenomena)”* (Presentation to the British Neuropsychiatry Association, St Anne’s College, Oxford, December 2008).

The interventions used in the PACE Trial were not supportive (such as the psychological support that may be offered to someone to help them cope with a devastating neurological disorder) but, as confirmed by Professor Simon Wessely, they were directive. Wessely has publicly stated: *“CBT is directive – it is not enough to be kind or supportive”* (New Statesman, 1<sup>st</sup> May 2008), and the interventions (CBT and GET) were specifically designed to disabuse participants of their (correct) belief that they suffer from an organic illness. That is unethical.

To inform patients that their symptoms are not the result of organic pathology when the symptoms of ME/CFS are caused by organic pathology is, without doubt, unethical.

(ii) Specialist Medical Care (SMC)

In The Lancet article, White states about SMC (Specialist Medical Care) in Panel 1: *“SMC was provided by doctors with specialist experience in chronic fatigue syndrome (webappendix p 1)”*.

The group known as the SMC (Specialist Medical Care) was originally to be called “Usual Medical Care” but was changed to “Standardised Specialist Medical Care” (SSMC). At the Joint Meeting of the Trial Steering Committee and Data Monitoring and Ethics Committee held on 27<sup>th</sup> September 2004, the Minutes record that: *“Stella Harris (Dr Stella Harris, patient representative) asked for an explanation as to why the name of the medical care treatment for the trial had now been altered to Standardised Specialist Medical Care (SSMC).... It was explained that...the term ‘specialist’ refers to the fact that the patient will be seen by a CFS specialist in the clinics”*.

The SSMC Manual states: *“SSMC should be the usual medical care that one would reasonably expect clinic doctors experienced in the assessment and treatment of CFS/ME to provide* (how *“usual medical care”* can suddenly be regarded as *“specialist medical care”* was not clarified).

Potential participants were assured that they would be receiving *“specialist medical care”* from *“clinic doctors experienced in the assessment and treatment of CFS/ME”*, which implies that participation in the PACE Trial would afford them specialist medical care **that is not available elsewhere.**

According to Hawkins and Emanuel (Hastings Centre Report 2005:35:5), there is an ethical problem if trial participants are misled into thinking they will receive better care than is available elsewhere: ***“Concern may arise if the subject believes falsely that she will receive more personal medical benefit than is possible under the circumstances”***.

Naming one arm of the trial “SSMC” was inaccurate because it gave the impression that participants would indeed be receiving specialist medical care (ie. the best medical care available), which clearly is not the case as “SSMC” consisted of doing nothing at all apart from a CFS Clinic doctor handing out a leaflet and giving general advice about balancing activity and rest and offering antidepressants.

Indeed, Page 6 of the SSMC Manual states: ***“The first SSMC appointment takes place within one month of randomisation. Participants will be seen by their SSMC doctor on a minimum of two further occasions in the 12 months after randomisation...Each session ...would commonly last about half an hour”*** (so participants receiving SSMC alone may have seen the Fatigue Service clinic doctor only three times for 30 minutes each time during their participation in the trial, a total of 90 minutes throughout the trial, which purports to constitute ***“specialist medical care”***).

Clearly, participants in the SMC group (indeed, all participants, because all received SMC) were misled into believing that they would be receiving excellent medical care from an “experienced” ME/CFS “specialist”, but this was not the case.

It is stated that in the SMC arm of the PACE Trial the PIs used 4 GPs, 7 infectious disease physicians, and 27 liaison psychiatrists (of whom 22 were from the same centre). Of the liaison psychiatrists, only 4 of the 27 had completed their training, the remaining 23 were trainees.

“Trainees” cannot legitimately be considered to be knowledgeable “medical specialists” experienced in the care of people with ME/CFS, so participants were deceived.

The Lancet may wish to ascertain from Professor White why such deception occurred in the PACE Trial.

In the Web Appendix Table A it is stated that the GPs in the SMC arm had a “special interest” in ME/CFS, but having a “special interest” does not denote knowledge of ME/CFS or experience in the care of people with ME/CFS.

Remarkably, information on ***“years of post-qualification experience”*** and whether practitioners had ***“previous experience in a CFS or chronic pain service”*** is provided for the CBT, GET and APT arms of the trial, but is left blank in respect of the SMC arm.

A further curious feature of the information that is presented in web appendix table A is that 22 of the 27 liaison psychiatrists were from one PACE Trial centre. There were a total of seven PACE Trial centres across six locations, so this would leave - at most

- the remaining 4 liaison psychiatrists and the 11 other physicians to provide SMC *to all participants* at the other centres. The web appendix also states that the 27 liaison psychiatrists (including 23 trainees) provided SMC to 29% of PACE trial participants, the 4 GPs to 23% of participants, and the 7 infectious diseases physicians to 47% of the participants. (It would be interesting to compare outcomes on SMC alone and indeed among the other groups, depending on which type of physician provided the “SMC” element.)

Furthermore, two of the “specialist medical care doctors” are named in The Lancet article as being (psychiatrists) Alastair Santhouse and Simon Wessely. The latter does not believe that ME exists (see Appendix 1) and in 2004 the former published “The 10 chronic fatigue syndrome commandments” (Doctor, 26<sup>th</sup> February 2004) in which he stated: “*CFS is the accepted name among professionals but many patients still prefer the name ME. Attribution of illness to a purely physical cause appears to predict a poorer response to treatment....The best research evidence is for CBT and/or a graded exercise programme*” and is on record as asserting: “*Psychiatry is the noblest branch of medicine*” and as stating of himself: “*At times I am carried away by the nobility of my calling*” (BMJ 2005:337:a2331).

Given that it is unethical to deceive participants in a clinical trial, one can only wonder what degree of expert specialist medical care the participants in those two SMC groups experienced.

### (iii) Pacing versus adaptive pacing therapy (APT)

All research guidance stipulates the ethical requirement for participants to be treated with respect and openness, but participants in the PACE Trial were not accorded such respect and were actively deceived over the nature of one of the interventions (APT).

Participants were misled by the PIs about the nature of the PACE Trial in that participants believed they were entering a trial testing the efficacy of pacing; they may thus not have been in a position to give fully informed consent. Since patients with classic ME/CFS quickly work out for themselves that in order to survive they have no alternative but to pace themselves, it does not need a £5 million study to prove that pacing is helpful. Pacing is the application of common sense, not a medical intervention.

All three PIs of the PACE Trial, Professors Peter White, Trudie Chalder and Michael Sharpe, are known to be strongly opposed to pacing and the Chief PI, Professor White, has publicly admitted conflicts of interest about it.

In 2002 the BMJ reported that Peter White and Trudie Chalder withdrew from the CMO’s Working Group on CFS/ME because the Report played down the psychosocial aspects of ME/CFS and concentrated on a medical model; worse still from their perspective, pacing was given equal status to CBT and GET. The BMJ reported that: “*Some clinicians believe it could perpetuate the condition*” (Chronic fatigue report delayed as row breaks out over content. Lynn Eaton. BMJ 5<sup>th</sup> January 2002:324:7). Two weeks later the BMJ reported: “*The clinicians argued that the psychosocial side of the condition should have had greater emphasis and were*

*concerned that ‘pacing’...was included as a form of treatment....Michael Sharpe....added that doctors would not accept pacing as a treatment just because it was recommended in the report” (BMJ 19<sup>th</sup> January 2002:324:131).*

Peter White further stated his opposition to pacing: *“The theoretical risk of pacing is that the patient remains trapped by their symptoms in the envelope of ill-health”* and that he resigned because he had a conflict of interest; he acknowledged the support of Professor Sharpe (Postgraduate Medical Journal 2002:78:445-446).

Whilst the PACE Protocol mentions the CMO’s Working Group Report, in their Lancet article White et al fail to mention their own conflicts of interest over pacing.

For all three PACE Trial PIs to have known conflicts of interest about one of the interventions supposedly being tested in the PACE Trial and to be strongly opposed to that intervention casts serious doubt on the validity of their finding that pacing does not work. Professors White and Sharpe’s published views on pacing are incongruous with the stated aim and the necessary impartiality of the PACE Trial.

It is therefore necessary to be aware that Adaptive Pacing Therapy (APT) used in the PACE Trial is very different from pacing as practiced by patients with ME/CFS. APT as used in the PACE Trial is a vehicle for incremental aerobic exercise and involves planning, achieving and sustaining targets. The CBT Therapists’ Manual states about APT: *“Activity is therefore planned”*, which indicates a structured activity regime, and the APT Therapists’ Manual lists other requirements for APT including *“plan set activity in advance”* (so activity must be *“set activity”*, not simply what the patient may be capable of doing at the time); there must be *“activity analysis”*; APT participants must *“constantly review model, diaries and activity”* and there is the requirement to *“involve relatives”*, which is nothing like pacing, ie. “doing what you can when you can”.

The Lancet article seriously misleads readers because the authors state: *“Our results do not support pacing, in the form of APT, as a first-line therapy for chronic fatigue syndrome”*. From his published record, Professor White was never going to support pacing, but it is improper to refer to APT used in the PACE Trial as “pacing”; the two are not the same, and other impeccable research (for example, Leonard Jason et al; AAOHN May 2008:56:5) has found pacing to be beneficial for people with ME/CFS.

(iv) Participants in two of the four groups were informed that “recovery” was possible with those interventions

The PIs and the CBT/GET therapists promoted CBT and GET as “curative” during the life of the PACE Trial. It is a basic rule of any clinical trial that participants are not told during the trial how effective is the intervention that they are receiving, but this was not complied with in the PACE Trial: for example, participants in the CBT group were informed on five separate occasions in their own CBT Manual that they can *“overcome their CFS/ME”* (ie. they can expect to be cured) by the application of CBT.

The trial therapists' engagement with participants was specifically directed at achieving the desired outcome of the trial by publishing and promoting glowing reports from trial participants during the trial and by invoking them to praise the trial to their friends and contacts and to influence and encourage those contacts also to enter the trial. To do so is unethical.

**It should never be suggested to trial participants that the intervention they are undertaking is a cure unless it is certain that it is indeed curative, in which case there would be no need for a clinical trial to prove the efficacy of the intervention.**

The Principal Investigators are on record as stating that full recovery from ME/CFS is possible with CBT/GET: Professor Michael Sharpe asserted: "*There is evidence that psychiatric treatment can be curative*" (BMB 1991;47:4:989-1005) and during the life of the PACE Trial Peter White has unambiguously asserted: "*recovery from CFS is possible following CBT....Significant improvement following CBT is probable and a full recovery is possible*" (Psychother Psychosom 2007;76(3):171-176).

**To mislead participants in a clinical trial by suggesting that a cure can be expected when there is no such certainty is in breach of the General Medical Council Regulations as set out in "Good Medical Practice" (2006):**

"Providing and publishing information about your services – paragraphs 60-62

*60. If you publish information about your medical services, you must make sure the information is factual and verifiable.*

*61. You must not make unjustifiable claims about the quality or outcomes of your services in any information you provide to patients. It must not offer guarantees of cures, nor exploit patients' vulnerability or lack of medical knowledge".*

To imply that patients can recover from ME/CFS if they would only follow the Wessely School psychiatrists' recommended regime of CBT/GET offers false hope: the recovery statistics simply do not support such a belief. The promise of a likely cure through CBT and GET is a cause for concern and Professor Peter White has been warned on numerous occasions -- on one occasion by NICE -- about making such a promise.

For example, in his submission about the NICE draft Guideline (24<sup>th</sup> November 2006, comments on chapter 6, page 308), Peter White objected to NICE's position concerning recovery from "CFS/ME"; referring to the draft Full Guideline 188 6.3.6.16, he was unambiguous: "*These goals should include recovery, not just exercise and activity goals*", to which NICE's response was equally unambiguous: "*The statistics indicate that total recovery is relatively rare and the GDG felt that to include recovery as a goal may lead to disappointment*" and the Final Guideline was clear: "*The GDG did not regard CBT or other behavioural therapies as curative or directed at the underlying disease process*" (Full Guideline, page 252).

To have informed selected PACE participants -- via the Trial manuals and therapists' instructions -- that they could "recover" with two of the four interventions being tested (ie. those in the CBT and GET groups), whilst APT participants were not given such advice (page 43 of the Full Trial Protocol states: "***APT will be based on the illness model of CFS/ME as a currently undetermined organic disease***") appears to have been seeking to bias the outcome in favour of the PIs' favoured interventions which, if successful, would support their belief in a psycho-social model of ME/CFS.

In the event, the PACE Trial results published in The Lancet do not support the PIs' psycho-social model of ME/CFS or their promise of a cure/recovery.

## 6. FAILURE TO "CONTROL" THE PACE TRIAL

The PACE Trial is described in The Lancet article as "***a randomised trial***", not "***a randomised controlled trial***".

The Lancet may wish to enquire as to why this element of the description has been dropped, since in his Trial Identifier, Peter White described the "Full Title" as "***Randomised Controlled Trial of CBT, graded exercise and pacing versus usual medical care for the chronic fatigue syndrome***" and at section 3.2 he enlarged upon that description: "***A four arm, single blind, randomised controlled trial in consecutive referrals of patients who meet operationalised criteria for CFS, with follow-up at 12 months***".

The purpose of "controlling" a trial is to ensure that any observed differences in outcomes can be confidently attributed to the intervention(s) being studied.

Was the PACE Trial adequately "controlled"? Certainly, there was no placebo control group, as with all such behavioural research studies, neither were participants nor purveyors of these interventions blinded.

There were three "active" arms (CBT, GET, and APT, all with concurrent "SMC"), and one non-active arm – the "Specialist Medical Care" without additional CBT/GET/APT, which was intended to act as a control group.

All participants would know which arm they had been recruited to, as would those involved in the conduct of the trial. Again, it is intrinsically difficult if not impossible to blind participants and purveyors of "therapy" – as compared with, for example, drug trials where a drug can be tested against a placebo in a double blind fashion.

However, these features have not mitigated against description of previous behavioural research trials as "controlled", reflecting efforts made to ensure that the intervention and control groups are appropriately matched.

Random allocation of participants to the various study and control (in this case, SMC) groups is implemented with a view to securing appropriately matched samples. But it does not, in itself, ensure that the study and control groups will be appropriately matched, thereby "controlling" the study.

It is noted that The Lancet article states: “***Because some errors were made in stratification at randomisation, we used true status variables rather than status at randomisation as co-variates***”.

It would therefore appear that, for reasons unspecified, the process of dividing recruited participants into homogeneous subgroups was subject to error.

The Lancet may wish to enquire as to how these errors came about, and to ensure that they are satisfied that the steps taken in the statistical analysis were sufficient to ensure that the comparisons made between the (apparently poorly controlled) participant groups involved in the PACE study are sufficiently robust.

## **7. ADVERSE EVENTS AND REACTIONS, AND SERIOUS DETERIORATION**

The incidence of adverse events reported in the course of the PACE Trial was remarkably high, the proportions having experienced an adverse event deemed by trial scrutinisers to be “non-serious” were CBT Group 89%; SMC and GET groups 93%; and APT Group 96%.

Far fewer adverse events deemed by scrutinisers to be “serious” were recorded (48, affecting 42 participants).

“Serious” adverse events were defined as: “***Death; Life-threatening event; Hospitalisation (excluding hospitalisation for elective treatment of a pre-existing condition); Increased severe and persistent disability, defined as a significant deterioration in the participant’s ability to carry out their important activities of daily living of at least 4 weeks continuous duration; Any other important medical condition which may require medical or surgical intervention to prevent one of the other categories listed; Any episode of deliberate self-harm***” (Lancet article, supplementary webappendix).

The Lancet article also reports adverse reactions (ie. adverse events deemed to be related to participation in the PACE Trial).

**Remarkably, only *serious* adverse reactions are reported. This means that we have no idea how many of the 3,002 adverse events that were deemed “non serious” may have been reactions to the trial interventions.**

Perhaps the most notable feature of the reporting on this subject is the stark contrast to stated commitments in the PACE Trial Protocol and PACE Trial Identifier, which repeatedly refer to study of all adverse effects of the interventions.

For example, both the PACE Trial Protocol and Trial Identifier state: “***We will also carefully monitor for any adverse effects of the treatments, and will undertake a detailed assessment, at home if necessary, for any subject who drops out of treatment for this reason, following which they will be offered appropriate help.***”

And the Trial Identifier further states: *“Adverse effects: Apart from finding out why subjects who prematurely stop their therapy did so, we will also administer the CGI, the SF-36 physical functional scale and the operationalised nine CDC symptoms of CFS/ME at all interviews, in order to monitor for significant set-backs.*

The Trial Protocol states: *“There is therefore a need for a trial that compares the relative effectiveness of supplementary therapies when added to standardised specialist medical care (SSMC) against SSMC alone, that seeks evidence of adverse effects, and that also examines predictors and mechanisms of response”* and *“The main aim of this trial is to provide high quality evidence to inform choices made by patients, patient organisations, health services and health professionals about the relative benefits, cost-effectiveness, and cost-utility, as well as possible adverse effects, of the mostly widely advocated treatments for CFS/ME”.*

It is further notable that the letter to general practitioners whose patients consented to be included in the Trial leads the doctor to believe that adverse effects – and not only serious adverse effect – will be studied: *“The purpose of the study is to compare the efficacy and adverse effects of four different treatments”.*

Similarly, responding to on-line comment regarding the PACE Trial protocol once the trial was underway, Professor White stated:

*“We have worked with the patient charity Action for M.E. to ensure we carefully measure and analyse adverse effects and reactions to all interventions. These are all assessed soon after they occur by senior clinicians experienced in CFS/ME, as well as being checked by other senior clinicians who are independent of all trial personnel, and who are masked to treatment allocation”* (<http://www.biomedcentral.com/1471-2377/7/6/comments/comments>).

The contrast between these statements and the report in The Lancet article is astonishing: *“Three scrutinisers (two physicians and one liaison psychiatrist who all specialised in chronic fatigue syndrome) reviewed all adverse events and reactions, independently from the trial team, and were masked to treatment group, to establish whether they were serious adverse events. Scrutinisers were then unmasked to treatment allocation to establish if any serious adverse events were serious adverse reactions.”*

Against this background, just ten adverse reactions are reported (Table 4 – safety outcomes).

However, participants have come forward – unsolicited – with disturbing evidence.

One PACE Trial participant, a professional person with a mental health background, has provided a statement dated 8<sup>th</sup> February 2011 saying:

*“Mr (name) was a research therapist for the PACE trial for both Edinburgh and Oxford.*

*“I was randomly selected to engage in the CBT aspect of the PACE Trial (and) Mr (name) was my ‘therapist’. Since it became very clear to me throughout my participation in the trial that Mr (name’s) prime concern was to obtain the desired results in keeping with preconceived views held by Sharpe et al, after 6 sessions I decided to disengage from the trial.*

*“In response to me disengaging, Mr (name’s) behaviour was totally unethical and unprofessional, and my complaint regarding this to Professor Sharpe was totally ignored.*

*“...it was quite obvious by Mr (name’s) response to any contentious questions I asked re: the manuals etc that his sole aim was to obtain results in keeping with those held by Chalder and Sharpe et al.*

*“I have since discovered that Mr (name) is a provider for insurance companies – as is clearly stated in his profile for Harley Street Therapy (the document referred to states: “he is a recognised provider for the majority of healthcare insurance Providers”). This is surely of immense significance in relation to the PACE Trial, as how could (he) have been objective in his role as research therapist when he is a provider to insurance companies. Is it any wonder that (he) took umbrage to any questions I asked re the efficacy and objectivity of the trial when it is likely he was using the trial as a stepping stone to further his career ambitions”.*

The same person had previously published a statement (New Scientist Opinion 13<sup>th</sup> March 2009), which said:

*“In desperation I even engaged in the CBT via the PACE Trial, which was quite obviously trying to manipulate the results and if anything, was exacerbating my symptoms”.*

In yet another statement, the same person reported:

*“The therapist misled me by saying he had a 99% recovery rate. He could not answer basic questions as to how he measured recovery.*

*“After I told the therapist that I was disengaging from the trial, he phoned me three times to attend a meeting with him -- although it states that you can leave the trial at any time and don’t even have to give a reason....He was very angry and defensive at the meeting due to me disengaging; he obviously had pressure on him to keep his numbers up – but that was no reason to treat me in such a way.*

*“It was quite apparent during the six sessions I had with the therapist that he was more interested in his research findings than in helping me.*

*“All in all, I found the whole experience to be quite damaging, particularly as my expectations were falsely raised and the therapist behaved quite unethically at the last meeting – no doubt due to pressure upon him to get the desired results”.*

Another participant wrote: *“I took part....I collapsed on week 3....Several of us had serious relapses. And when I was reduced to lying in bed every day, in pain, unable*

*to do a thing for myself, these researchers did not want to know, believe me. I was on my own when it came to trying to undo the damage”.*

*A different participant wrote: “I took part in this study, and was randomised to the GET group, and I’d be very sceptical about its results. My initial blood tests showed some signs of infection and inflammation so I was sent for another set which apparently didn’t, so I could be accepted into the trial. The assessment/criteria forms which had to be filled out before and during the trial did not mention symptoms after exercise or delayed onset fatigue; there was very little attention paid to pain....At the start of the trial, I had to wear an (actometer) thing for a week, presumably to measure activity levels. But at the end of the trial, this wasn’t repeated. The fitness tests measured the number of steps I could do in a set amount of time, but paid no attention to the fact that I usually couldn’t walk for two days after these assessments”.*

*Another person commented: “The crunch came today when I went to see my physio who has been part of the PACE trial....On a physical level, I feel worse now than when I started seeing her. She is putting this down to my ‘poor’ management and that fact that I’m allegedly not following her instructions to the letter. I am trying but my condition fluctuates so much that it is impossible to stick to a consistent routine and I am not pushing myself just for the sake of ticking her boxes. I am trying my best but it doesn’t seem to be good enough.*

*“I just wanted to cry after the appointment...I can’t help my state of health and I am not deliberately doing things that set me back.*

*“I keep detailed diaries about food intake, time, activity and mood but just can’t find any patterns, even though I’m told there must be some. There just aren’t.*

*“She sells me lots of success stories about other patients who have been through the GET programme and are now fully functioning. She tells me I can get there too....She is so positive about this that she isn’t at all tuned in to my needs and current state.*

*“The lectures I get are because she thinks she’s is motivating and helping me, whereas I just feel told off and criticised. Who wouldn’t when they are just told...’You need to be stricter with yourself or you won’t improve....You’ve got to believe in this; you have to work harder at it; I don’t think you really believe in this and that’s why it’s not working’?*

*“I also don’t want to feel bullied, lectured, useless and reduced to tears on a regular basis following a session.*

*“I have now made an informal complaint and discussed my experiences with the service lead....(She) said that GET has a one in three success rate and that I clearly fell into the two people that don’t respond to it”.*

These are disturbing accounts, of which there are many more on the internet.

**It is, furthermore, a matter of concern that PACE Trial participants were instructed not to consult a clinician if they experienced a worsening of symptoms during the trial (Therapists' Manual on CBT, p 28-29).**

Consideration of the nature of the ten “serious adverse reactions”, as presented in the supplementary webappendix to The Lancet article, is illuminating. Almost all are mental health problems, which underlines concerns regarding the nature of the disorder(s) from which PACE Trial recruits were suffering. It also raises interesting questions about the nature and impact of the interventions being purveyed – for example, the two “serious adverse reactions” to SMC were *“worse [CFS] symptoms and function”* and *“increased depression and incapacity”*.

Finally, the data on withdrawals due to worsening is not reported separately in The Lancet article, but is combined into a composite measure representing serious deterioration:

*“Serious deterioration in health was defined as any of the following outcomes: a short form-36 physical function score decrease of 20 or more between baseline and any two consecutive assessment interviews; scores of much or very much worse on the participant rated clinical global impression change in overall health scale at two consecutive assessment interviews; withdrawal from treatment after 8 weeks because of a participant feeling worse; or a serious adverse reaction”.*

A total of 52 PACE Trial participants (8.1%) experienced a “serious deterioration” according to this measure, and it is reported that rates of serious deterioration did not differ between treatment groups. However, the rates of withdrawal due to worsening are not specifically reported, so we do not know whether or how withdrawals from the Trial due to worsening differed between the different intervention groups.

Relatedly, it is unclear whether or not adverse events experienced by people who subsequently dropped out of the PACE Trial are included in the published figures. It is possible that a participant may have dropped out of the trial due to adverse events without the relevant adverse event featuring in The Lancet report.

## **8. CHANGES TO ENTRY CRITERIA**

The Principal Investigators diluted the entry criteria after the PACE Trial had commenced in two respects:

- by raising the SF-36 physical function score threshold and
- by including people who had previously undergone CBT/GET, provided this was not conducted at a PACE Trial centre

The impact of these changes was not negligible. Among the first 140 people referred as potential participants, the Investigators had excluded almost half (65; 46.4%) on the grounds that they scored too highly on the SF-36 physical function scale (36 people; 25.7%) or had previously undertaken an intervention that was on offer in the PACE Trial (29 people; 20.7%).

### Changes to the Physical Function Threshold

The short form-36 (SF-36) physical function scale runs from 0-100, with higher scores indicating better physical functioning. In the PACE Trial Identifier, the SF-36 cut-off point for entry to the PACE Trial had been set at the remarkably high score of 75. However, when recruiting began a threshold of 60 was adopted. Later, because of recruitment difficulties, ***“this requirement was changed from a score of 60 to a score of 65 to increase recruitment”*** eleven months after the trial began. (These thresholds are still relatively high, meaning that people with relatively good physical function could be recruited.)

This meant that the trial now included people with better physical functioning scores at baseline than those recruited at the outset. While it is a most unusual situation in any clinical trial for the first tranche of participants to meet different entry criteria from those who were recruited later, this particular change was of key significance in that scores recorded on this same scale played a vital role in assessing outcomes, and people who had higher scores on this scale at baseline would require less change during the course of the trial to attain a relatively high score on completion. They may also have been less ill and therefore better able to engage with CBT and exercise than people who attained lower physical function scores at the outset.

This change has important implications for the analysis of the results (which are considered below).

### Changes to eligibility if prior involvement in PACE Trial interventions

Another change to the recruitment criteria that pertained at the start of the trial was the decision to include people who had previously received a trial intervention on the grounds that the PACE Investigators ***“found the nature of treatment given elsewhere hard to establish”***. This appears a curious rationale, as it would have been perfectly feasible to continue to exclude anyone who had previously undergone any intervention that involved or purported to involve CBT and/or graded exercise, whether or not they could be sure that this was the same form of these interventions as was involved in the PACE trial. In the event, the decision was to exclude only people who had ***“previously received a trial treatment for their present illness at a PACE clinic”***.

Like the decision to recruit people with a higher level of physical functioning, this change would, of course, have had the impact of widening the pool of potential recruits at a time when the PACE trial was finding recruiting significantly slower than anticipated.

## 9. CONSIDERATION OF THE DATA ON OUTCOMES

### Statistically significant outcomes

“Statistical significance” is a measure of the likelihood that the observed outcomes occurred by chance alone. There is said to be a “significant” difference between groups if the likelihood of the difference recorded having occurred by chance is low. The conventional threshold for statistical significance is 95% (commonly expressed as a “probability” [p] value of 0.95). In other words, if the likelihood of an observed difference between an intervention and a control group having occurred by pure chance is 5% (1 in 20) or less, then the result may be described as “statistically significant”.

The PACE trial article in *The Lancet* reports several statistically significant outcomes for the CBT and GET intervention groups over the SMC-alone group. However, it is relevant, in interpreting these reported findings, to be aware of the fact that the comparison is of mean (ie. average) outcomes for the groups as a whole. Within that average there can be a wide variation in the actual outcomes recorded on a participant by participant basis.

That this was so in the PACE Trial is indicated by the relatively large size of the “standard deviations” recorded – the “standard deviation” being a measure of the extent to which observed outcomes tended to vary from the mean. This would be entirely in keeping with the emergence of variable outcomes *within* the groups, which in turn would be in keeping with variable impact reflecting the heterogeneity of the trial cohort.

It is further notable that, without exception, in all groups, the standard deviations on both primary outcome measures *increased* following commencement of the PACE trial, and with one exception (the SD in respect of the GET group scores on the fatigue scale was 7.5 at 12 weeks into the trial, and still 7.5 at 52 weeks), had increased further by the time of final assessment. This means that the spread of participants’ rating scores within the group – on the “fatigue” and “physical function” scales - *increased* following the PACE interventions.

However, the standard deviations (specified in Table 3) are not mentioned at all in the text of *The Lancet* article, so there is no consideration by the authors of their possible significance.

It should also be noted that in cohorts the size of the PACE Trial (approx 160 in each of the four arms of the trial), relatively small differences can emerge as “statistically significant”, and emergence as “statistically significant” can hinge on the observed outcomes in respect of relatively few participants.

Furthermore, differences that are statistically significant are not necessarily significant in clinical terms (clinical significance is considered below).

### Confidence in Observed Differences Between Groups

The width of the confidence intervals given in respect of the “primary outcomes” on the PACE trial data may indicate that levels of confidence in terms of the validity of the observed significant differences is relatively poor. Confidence intervals are not

discussed in The Lancet paper, but are presented in Table 3 -- see figures re: "(95% CI)".

For example, when comparing the CBT group with the SMC-alone group, at 52 weeks, the mean fatigue scores are reported as having been 3.4 points lower for CBT, with a 95% Confidence Interval of 1.8 to 5.0. This is a wide confidence interval in relation to the (relatively small) effect size, indicating that the study's data is unreliable.

**Every study must be judged in terms of its external validity ie. the transferability of the results to a non-study population. In this study, neither p (probability) values nor confidence intervals indicate that the findings may legitimately be viewed as externally valid. The external validity of the PACE study is seriously undermined by these considerations.**

The error bar overlap is another measure of whether or not one can be confident that any differences in observed outcomes between groups are meaningful. In The Lancet article the relevant data are illustrated in Figure 2. The vertical bars indicate the margin for error around the recorded mean data points. It is clear from this presentation that the error bars in respect of the mean recorded outcomes for the various groups overlap at a number of points. This indicates a lack of confidence in these observed differences once this margin for error is taken into account. For example, the outer limits of the error bars of the average fatigue data reported in respect of each of the four PACE Trial groups at 24 weeks (ie. "post-therapy") overlap – so one cannot be confident that the observed differences in mean effect sizes are valid.

It is notable that this issue is not discussed in the PACE trial article. Indeed, even in the graphic illustration [figure 2] there is no mention of the term "error bar", nor any alternative descriptor of these bars. However, having referred to Figure 2 as showing "profiles for the primary outcomes", the article immediately continues: ***"In the final adjusted models (figure 3), participants had less fatigue and better physical function after CBT and GET than they did after APT or SMC alone"***.

#### Clinically Useful Difference

The authors' attempt to consider the clinical significance of their data hinges on a particular definition of "clinically useful difference": ***"A clinically useful difference between the means of the primary outcomes was defined as 0.5 of the SD [standard deviation] of these measures at baseline, equating to 2 points for Chalder fatigue questionnaire and 8 points for short form-36"***.

Against this background, the authors are able to report: ***"Mean differences between groups on primary outcomes almost always exceed predefined clinically useful differences for CBT and GET when compared with APT and SMC"***.

Why ***"almost always"***? And why ***"when compared with APT and SMC"***?

The relevant figures are presented in Table 3. A basic appraisal suggests that the differences between the average for CBT, and for GET, as compared with SMC on one of the two primary outcomes - physical function - were not “clinically useful”, at 7.4 points and 6.9 points, respectively.

However, given that the groups differed on average score at baseline, it may be more appropriate to consider whether the changes over the course of the study differed by more than 8 points. (The GET Group had a lower mean score on this measure at baseline than the SMC Group, meaning that they would have to make more progress just to catch up - a possible failure of “control” in this trial). Against this background, the GET figure becomes “clinically significant” against SMC alone. The CBT Group change remains below the threshold of clinical significance.

The incorporation of an additional parameter – ie. comparison with the APT Group - at a stroke both doubles the number of comparisons made, and introduces comparison with a group that had a poorer mean outcome on this particular measure (with an average of 45.9 points as opposed to the 50.8 recorded in respect of the SMC Group). **In this way the authors are able to conjure up a positive statement regarding the clinical significance of their data.**

Furthermore, it is difficult to see how the “mean difference from SMC” figures presented in Table 3 have been calculated. They do not entirely square with the mean figures presented for the various groups at baseline and 52 weeks, from either of the perspectives of calculation described here.

For example, the mean score at final analysis for Physical Function among the SMC Group was 50.8, a rise of 11.6 points over the baseline mean of 39.2. For the APT Group, the respective figures are 45.9 and 37.2, representing a rise of 8.7 points. So this is 2.9 points less than the respective change among the SMC Group. The figure presented in the Table for “mean difference from SMC”, however, is -3.4. On the other hand, a simple comparison of the means between the two groups at final analysis gives a difference of 4.9 points less for APT. (45.9 as compared to 37.2). Again, this does not square with the figure of -3.4 that is presented in the Lancet article. There are several other such apparent discrepancies.

The clinical significance of the findings is further undermined by consideration of the data below.

#### “Normal” Function

Consideration and appraisal of participants’ outcomes in the PACE Trial was focused on two “primary outcome measures”. These concerned ratings recorded on the short form-36 (SF-36) physical subscale, and the Chalder Fatigue Questionnaire (CFQ). These were combined with a view to giving an indication regarding the important issue of the number of participants who were deemed to have attained “normal” function.

Remarkably, certain ratings that would qualify a participant as sufficiently impaired to enter the PACE trial would also be considered as indicating “normal” function on completion of the trial. This was defined as follows:

*“In another post-hoc analysis, we compared the proportions of participants who had scores of both primary outcomes within the normal range at 52 weeks. This range was defined as less than the mean plus 1 SD scores of adult attendees to UK general practice of 14.2 (+4.6) for fatigue (score of 18 or less) and equal to or above the mean minus 1 SD scores of the UK working age population of 84 (-24) for physical function (score of 60 or more)”.*

**Thus the threshold score to qualify for consideration as “normal” on physical function at the conclusion of the trial (60) was identical to the threshold for entry at the start of the trial (60) and below the threshold for entry as subsequently raised during the course of the trial (65).**

Similar considerations apply in respect of the other primary outcome measure – the “Chalder Fatigue Scale” rating.

On the key issue of the determination of those who had “normal” fatigue in reporting outcomes, the definition used was a Likert-scored CFQ score of 18 or less. However, people who achieved such Likert ratings could score up to 9 if the same responses were recorded bimodally.

Yet, according to the PACE Trial Protocol, a bi-modal score greater than 3 represents abnormal fatigue and indeed a score of 6 or more is one of the Trial's entry criteria.

**Thus, as with the SF-36 physical function score, it was possible for a participant to have a fatigue rating that was both “normal” and “abnormal” depending on which of these definitions is applied.**

Indeed, identical responses could both qualify a person as sufficiently “fatigued” for entry to the PACE trial and later allow them to be deemed to have “normal” levels of fatigue. What’s more, as with physical function, it would be possible for a person to record a poorer score on the CFQ on completion of the trial than at the outset, yet still be deemed to have attained “normality” on this primary outcome measure.

**Surely it cannot be acceptable to describe PACE participants as having “normal” levels of fatigue and physical function when they could simultaneously be sufficiently disabled -- as judged by their levels of fatigue and physical function -- to have qualified for entry into the PACE Trial in the first place?**

**This is a most unusual situation in a clinical trial.**

**It is astonishing that such a manifest contradiction survived The Lancet’s peer review process.**

### The SF-36 Physical Function Score

The definition of “normal” physical function is problematic in other respects. The threshold SF-36 score denoting “normal” fatigue – ie. 60 (see quote above) – is based on a mean score of 84 for *“the UK of population of working age”*. However, consideration of the cited source in the Protocol makes it difficult to see how this figure has been obtained (Jenkinson C et al. BMJ 1993:306:1437-1440). Moreover, the cited paper indicates that the appropriate comparison should be with a higher figure, which would reduce the number of PACE Trial participants who could be deemed to have attained “normal” fatigue.

The paper cited in the Lancet article for the mean of 84 on the SF-36 physical function scale (Bowling A et al; J Publ Health Med 1999:21:255-270; ref 33 in The Lancet article) provides data from three different sources, including the source cited in the PACE Trial protocol. These data sets give respective means of 92.5, 92.7 and 91:

- One of the three data sets is from a 1993 paper, which gave a mean SF-36 score of 92.5 for adults of working age without long-standing health problems
- The second data set gives a mean SF-36 score of 92.7 for adults of working age without a long-standing health problem; when including those with a long-term health problem and all adults, the mean score falls to 89.6
- The third data set presents a mean SF-36 score for adults of all ages without long-standing illness of 91.

In the light of these figures in the cited reference source, the use of a mean score of 84 for *“the UK population of working age”* to calculate the threshold of “normal” fatigue appears inexplicable.

The SF-36 score of 84 that is presented in The Lancet article as the mean score for the UK working age population may relate to all adult ages (ie. working age *and* elderly people). Also, it would appear to include individuals with long standing illness.

For the purpose of comparing recorded SF-36 outcomes of PACE Trial participants, it would be appropriate to gauge their results against the SF-36 scores of the healthy adult population.

Furthermore, Professor White presents incongruous information on this subject in the PACE Trial Identifier, the PACE Trial Protocol, and the Lancet paper, as he states that the mean SF-36 score used to calculate “normal” fatigue was **“90”**, **“about 85 depending on the study”**, and **“84”** respectively.

Thus, with each successive document, the figure used to calculate the threshold of the “normal” range of physical function for the purposes of appraising the PACE Trial outcomes has been reduced, increasing the likelihood that PACE trial participants’ score may be deemed “normal” on conclusion of the Trial.

In the PACE Trial Protocol and the PACE Trial Identifier, it is stated that “*a positive outcome*” and “*normal function*” requires a score of 75 or more. Therefore, for the same criterion – the threshold of the “normal” range - Professor White provides two different benchmarks: 60 - as applied to analyse recorded results, and 75 - as stipulated in the PACE Trial Protocol and Trial Identifier.

**It is suggested that Professor White be asked to clarify why he chose the lower of these figures, and to explain why a figure of 60, which would qualify a person as sufficiently low in physical function to be considered for entry to the PACE Trial, can accurately be described as “normal”.**

### The Chalder Fatigue Questionnaire

The “Chalder Fatigue Questionnaire” (CFQ) was produced by PACE Trial Principal Investigator Professor Trudie Chalder and Director of the CTU, Professor Simon Wessely, amongst others (J Psychosom Res 1993;37:2:147-153).

It sets out 11 questions. For each question, patients have to record one of the following four responses: (i) less than usual; (ii) no more than usual; (iii) more than usual; or (iv) much more than usual. Responses to all questions are then combined to provide an overall “fatigue” score. These responses can be scored in one of two different ways:

- (1) by according a separate score to each point on a scale (ie. “Likert” scoring)
- (2) by scoring responses (i) and (ii) as 0, and responses (iii) and (iv) as 1 (ie. “bi-modal” scoring).

The sole use of Likert scores on the CFQ to judge outcomes is striking. The CFQ played a part in determining eligibility for the trial, and bi-modal scoring was used in this context. Potential participants had to score at least 6 out of a possible 11 on the bimodally scored CFQ for entry to the trial.

According to the Trial Protocol, a similar approach was to have been taken to the analysis of outcome measures:

***“Primary Efficacy Measures: We will use the 0,0,1,1 item scores to allow a possible score of between 0 and 11. A positive outcome will be a 50 % reduction in fatigue score, or a score of 3 or less, this threshold having been previously shown to indicate normal fatigue.”***

However, Likert appraisal was to be conducted as a “***Secondary Outcome Measure*”:**

***“The Chalder Fatigue Questionnaire Likert scoring... will be used to compare responses to treatment.”***

In the published paper, however, only analysis of the Likert scores is presented. Remarkably, the Lancet article states about this:

***“Before outcome data were examined, we changed the original bimodal scoring of the Chalder fatigue questionnaire (range 0-11) to Likert scoring to more sensitively test our hypotheses of effectiveness”***

thus implying that a decision was made to adopt a different approach, rather than to drop one of two proposed analyses.

It is notable that the analysis that was dropped was to have been a primary efficacy measure.

Moreover, if Likert scoring is known to be superior to bimodal scoring, Lancet readers may rightly wonder why Likert scoring was not to have been the primary measure in the first place.

It is noted in this connection that the PACE Trial’s sibling, the Fatigue Intervention by Nurses Evaluation (FINE) Trial, also used the Chalder Fatigue Questionnaire and that, on bimodal scoring, the FINE Investigators discovered that the results at the primary outcome point were not statistically significant. However, using post-hoc re-structured Likert scoring, the FINE Investigators were able to produce statistically - though not clinically - significant results.

It is further notable that the FINE paper is referenced at the brief “Research in Context” section of The Lancet article (Panel 2), but with absolutely no acknowledgement of the reported findings.

This is neatly skirted around by focusing the coverage on reviews and simply noting the existence of ***“two additional trials that were not included in these reviews”***, one of these being the FINE trial.

This is astounding. Given the close links between these two trials, it is inconceivable that the Principal Investigators on the PACE trial were unaware of the disappointing outcomes emerging from the FINE Trial, nor that a change from bi-modal to Likert type scoring on the CFQ had helped improve the reported results of the FINE Trial.

#### The six minute walking test

One of the secondary measures used was an ***“objective walking test”***, involving walking for six minutes.

The capacity of such a test to assess capacity in this disorder is highly debatable, as it fails to take account of the after effects of such exertion. The CMO’s Working Group Report of 2002 expressly warns of this:

***“Perhaps the prime indicator of the condition is the way in which symptoms behave after activity is increased beyond what the patient can tolerate. Such***

*activity, whether physical or mental, has a characteristically delayed impact, which may be felt later the same day, the next day, or even later...In some instances the person can sustain a level of activity for several weeks, but a cumulative impact is seen, with a setback after several weeks or more”.*

Moreover, the Chief Principal Investigator himself, Peter White, has published evidence supporting the need for serial post-exercise testing in CFS (JCFS 2004:12:(2):51-66).

The reference provided in The Lancet article regarding the walking test (Butland RJ et al; BMJ 1982:284:1607-1608) cites a further paper (McGavin CR et al; BMJ 1976:I:822-823) which draws attention to the difficulty of achieving reproducible results with such a test, stating that it needs to be carried out twice to achieve reproducible results. Unless this protocol was followed in the PACE Trial, then the test is invalid according to the reference cited. Moreover, the six minute walking distance test has been shown to be influenced by test familiarisation so is potentially unreliable (Gibbons WJ et al; Cardiopulm Rehabil 2001:21:(2):87-93).

Furthermore, the six minute walking test has low test/re-test reliability (especially as the assessors knew to which of the intervention groups the participants had been allocated in the trial, such masking being deemed *“impractical”* by the PIs).

In the PACE Trial, the mean 6 minute walking distance recorded at 52 weeks by those who had undergone CBT was 354 metres, representing a 21 metre increase from baseline, but one metre *less* increase – adjusted to 1.5 metres less increase -- than the SMC group who received no other intervention. (The SMC alone group increased by 22 metres from baseline.)

For those who had undergone GET the mean distance was 379 metres, representing a 67metre increase from baseline.

This distance over six minutes is notable, given that walking was commonly chosen as a GET intervention, which is described in The Lancet article as follows (panel 1):

*“... Target heart rate ranges were set when necessary to avoid overexertion, eventually aimed at 30 min of light exercise five times a week. When this rate was achieved, the intensity and aerobic nature of the exercise was gradually increased, with participant feedback and mutual planning. The most commonly chosen exercise was walking”.*

As with other PACE Trial results, it should be noted that the standard deviations – a measure of how widely individual results were spread around the mean – are substantial. For example, the 379 mean score in respect of the GET group was subject to a Standard Deviation of 100.

Normal scores on the six minute walking test are “puttering around the house” (320 metres); “easy health walk” (500 metres); “brisk walk” (650 metres) and “fast walk” (800 to 1,000 metres) (<http://walking.about.com/od/measure/f/howfastwalking.htm> ).

In a study entitled “*Six minute walking distance in healthy elderly subjects*” (T Troosters et al; Eur Respir J 1999;14:270-274), the mean walking distance for healthy people aged 50 to 85 years was shown to be 631 metres. A score of 518 metres was considered abnormally low for healthy but elderly people.

In other studies, patients with chronic obstructive pulmonary disorder (including those needing supplemental oxygen) were able to walk on average about 60 more metres during the 6 minute walking test compared with those in the PACE Trial who had received GET (<http://171.66.122.149/cgi/content/full/163/6/1395> ) and patients with pulmonary sarcoidosis achieved the same distance (379.7 metres) during the 6 minute walking test as PACE participants achieved in the GET group at 52 weeks (<http://www.thoracicmedicine.org/article.asp?issn=1817-1737;year=2009;volume=4;issue=2;spage=60;epage=64;aulast=Alhamad>).

PACE participants were able to walk less distance during the 6 minute walking test than people with traumatic brain injury (<http://www.oandp.org/academytoday/2009feb/2.asp> ).

PACE participants’ 6 minute walking test scores were also lower than scores documented in many other serious diseases such as those awaiting lung transplantation, where a six minute walking test of less than 400 metres is regarded as a marker for placing a patient on the transplant list (Kadikar A et al; J Heart Lung Transplant 1997;16(3):3130319) and those in chronic heart failure (whose mean score is 682 metres), those in heart failure class II (mean score 558 metres) and those in heart failure class III, whose mean score is 402 metres in six minutes (DP Lipkin et al; BMJ 1986:292:653).

**Against this background, the PACE Trial results can only be interpreted as clinically insignificant.**

**After CBT or GET, PACE Trial participants did not even achieve a six minute walking distance of 518 metres that is considered abnormal for healthy people aged 50-85 years.**

**None of the groups in the PACE Trial came anywhere near to recording a normal average walking score for the six minute walking test at 52 weeks.**

This feature – on the only “objective” outcome measure - is not highlighted in The Lancet article, which simply states:

***“6-min walking distances were greater after GET than they were APT and SMC, but were no different after CBT compared with APT and SMC”.***

Furthermore, as noted above, the PACE Trial walking test gives no indication for how long participants could maintain the walking speed beyond the 6 minute test, nor if they suffered from post-exertional malaise, nor an indication of participants’ walking ability over a longer time frame, or exacerbation of other symptoms.

## 10. **DATA NOT REPORTED / MEASURES DROPPED**

### Objective measure of activity in daily life

The PIs originally intended to obtain a non-invasive objective measure of outcome using post-treatment actigraphy (and obtained ethical approval and funding on this basis) but once the trial was under way the Chief PI abandoned actigraphy on the spurious grounds that wearing a small monitor round an ankle for a week would be too great a burden at the end of the trial. There is no mention in The Lancet article of the prior intention to use this measure.

Compared with the need to keep daily activity diaries, RPE (rating of perceived exertion) scores, goal sheets, exercise diaries, GET plans, progress sheets and other records, the wearing of an actigraphy monitor for a week at the end of the PACE Trial would not be at all onerous, so Professor White's reason for not adhering to the Protocol is risible. It is possible that he realised the PACE Trial would fail unequivocally if actometers were used, so he decided the risk was too great.

Responding to on-line comment regarding the published (shortened version) of the PACE Trial Protocol while the trial was still underway, Professor White stated: "***we decided that a test that required participants to wear an actometer around their ankle for a week was too great a burden at the end of the trial***". Given the number and degree of claims made for the efficacy of CBT and GET, it is not credible that the wearing of an actometer around the ankle for one week would be deemed too onerous at the end of the trial.

Professor White also made the following commitment regarding actigraphy: "***We will however test baseline actigraphy as a moderator of outcome***" <http://www.biomedcentral.com/1471-2377/7/6/comments/comments>  
This commitment has not been carried out in the article published in The Lancet.

Professor White also stated: "***We have used several objective outcome measures; the six minute walking test, a test of physical fitness, as well as occupational and health economic outcomes***".

The Lancet article neither reports participants' results on this "test of physical fitness" nor findings on the occupational and health economic measures.

It is noted that the "test of physical fitness" is referenced to a paper in geriatric medicine entitled "A self-paced step test to predict aerobic fitness in older adults in the primary care clinic" (Petrella RJ, Koval JJ, Cunningham DA, Paterson DH Journal of the American Geriatric Soc 2001; 49:632-8).

It is further noted that the occupational and health economic outcomes reference is for outcomes in mental, not physical, health (Costing mental health interventions. Beecham J et al. In: Thornicroft G, Measuring Mental Health Needs. London, Gaskell, 2001).

After spending millions of pounds of public money and involving hundreds of people in an intensive regime, the PIs failed to obtain a robust objective measurement or

outcome. Instead, the PIs chose a six minute walking test as ***“an objective outcome measure of physical capacity”***. The observations obtained on this measure were poor (to say the least), even though such a snapshot measurement would not be sufficient to capture post exertional debility. (Findings on the walking test are discussed above.)

Instead of using actometers, the PIs relied largely on participants’ subjective responses to questionnaires, which are notoriously unreliable. Subjective data is just that – it lacks objectivity and is prone to influences such as participant deference, motivation, gratitude, placebo effect and interpretation. Subjective data is not evidence-based and should be considered unreliable in remitting/relapsing disorders such as ME/CFS. Furthermore, to rely on subjective data in a trial that intentionally set out to modify participants’ own subjective beliefs cannot be classed as a scientific study.

A study from 1997 demonstrated the problem of using self-reported data in ME/CFS patients (Vercoulen JH, Bleijenberg G et al; J Psychiat Res 1997;31(6):661-673) . The rationale for that study was:

***“It is not clear whether subjective accounts of physical activity level adequately reflect the actual level of physical activity ....we evaluated whether physical activity level adequately can be assessed by self-report measures”***.

Vercoulen and Bleijenberg et al evaluated the correlations on seven outcome measures in relation to the actometer readings and demonstrated that ***“none of the self-report questionnaires had strong correlations with the Actometer”***. Having evaluated whether physical activity level can be adequately assessed by self-report measures, they found that ***“self-report questionnaires are no perfect parallel tests for the Actometer”*** and that subjective questionnaires ***“do not measure actual behaviour”*** because ***“responses may be biased by cognitions concerning illness and disability”***.

They continued:

***“In earlier studies of our research group, actual motor activity has been recorded with an ankle-worn motion-sensing device (actometer) in conjunction with self-report measures of physical activity. The data of these studies suggest that self-report measures of activity reflect the patients' view about their physical activity and may have been biased by cognitions”***.

One of these authors was the same Gijs Bleijenberg who co-wrote the Comment on the PACE Trial article for The Lancet, extolling the outcomes recorded on subjective report measures.

A study on (ME)CFS patients in the US that used CBT -- and which also encouraged activity -- found on actigraphy measurements that there was in fact a numerical *decrease* from the pre-treatment baseline (Friedberg F et al; J Clin Psychol 2009, February 1).

There is thus considerable evidence that alleged improvements reported in subjective questionnaires may not be reliable.

A significant point raised by a patient is that the PIs measured subjective changes in participants who suffer from what the Wessely School refer to as “*perceived disability*” (BMJ 2003:326:595-597). This means that on the one hand, the Wessely School believe that people with “CFS/ME” are unreliable in their own assessment of their disability (because the Wessely School assert that people with ME/CFS only “perceive” themselves to be ill and that they hold “aberrant illness beliefs”), yet on the other hand the Wessely School have based the outcome of a £5 million study on such patients’ personal assessment of their disability (ie. PACE Trial participants are deemed capable of accurately reporting their symptoms/disability). In other words, the PIs are satisfied that the only requirement to prove that CBT and GET are effective is for participants (whose judgment the PIs regard as suspect) to say that they are effective. Unfortunately, the objective measures required to expose the PIs’ double standards (actometers) are notable by their absence.

#### Client Service Receipt Inventory

Whilst the most important objective primary outcome measure was abandoned during the trial, an important secondary outcome measure was not reported at all by the authors. The Protocol stated:

***“The Client Service Receipt Inventory (CSRI), adapted for use in CFS/ME, will measure hours of employment/study, wages and benefits received, allowing another more objective measure of function”.***

On the advice of (now) Professor Sir Mansel Aylward, former Chief Medical Advisor to the DWP, the Department for Work and Pensions co-funded the PACE Trial because it wanted a therapy that would get people with ME/CFS off State benefits and back to work.

By letter dated 17<sup>th</sup> March 2011, the DWP Central Freedom of Information Team (re)confirmed that the PACE Trial was the only clinical trial funded by the DWP and supplied the reason for doing so: ***“The funding was agreed by a previous Departmental Chief Medical Adviser, who supported PACE due to his combined expertise and academic interest in this area of work. In his role as Chief Medical Adviser he felt it reasonable to support this trial, particularly as when the trial was initially being developed, consideration was given to exploring the use of a five point measure of work and social adjustment, which would look at employment and social outcomes for people taking part in the trial”.***

By letter dated 21<sup>st</sup> February 2011, Dr Frances Rawle, Head of Corporate Governance and Policy at the MRC, provided more information about the involvement of the DWP:

***“You ask why questions relating to participants’ financial situation were included...We accept that this is unusual in a clinical trial but...being in receipt of***

***a disability pension was amongst a group of factors found in previous work (ie. a “finding” made only by the Wessely School) to be potential predictors of a negative outcome to treatment... The other reason to include financial questions was to be able to measure how treatments affected both healthcare costs and costs to society”.***

Peter White collected the data but has not delivered what was required as he has not published the number of participants who were able to return to gainful employment or study at the conclusion of the PACE Trial.

This must be disconcerting for Aylward, who upon leaving his post at the DWP immediately became Director of the UNUMProvident (permanent health insurers) Centre for Psychosocial and Disability Research at Cardiff University (for evidence of Aylward’s involvement with and inflexible views about the nature of ME/CFS, see <http://www.meactionuk.org.uk/magical-medicine.htm>).

On 18<sup>th</sup> February 2011, the day the PACE results were published by The Lancet, the Information Officer at the Irish ME/CFS Association (Tom Kindlon) sent Professor White an email noting that this had not been reported and politely requesting this data; he has not received the courtesy of a reply from Professor White.

Since White et al withheld this data, it can only mean that the PACE Trial interventions had no positive outcome in that respect.

#### Impact of Clinician Expectations

Responding to on-line questions regarding possible bias arising from the known affiliations of the PACE Trial Investigators, Professor White stated: ***“To measure any bias consequent upon individual expectations, all staff involved in the PACE trial recorded their expectations as to which intervention would be most efficacious before their participation, and we will publish these data after the end of the trial”*** (<http://www.biomedcentral.com/1471-2377/7/6/comments/comments>).

It is noted that this has not been done in The Lancet article.

#### “Recovery”

When the Protocol was published, it contained Peter White’s definition of recovery that was to be used in reporting the results of the PACE Trial:

***“10.2.1 Secondary efficacy measures ... 4. "Recovery" will be defined by meeting all four of the following criteria: (i) a Chalder Fatigue Questionnaire score of 3 or less; (ii) SF 36 physical Function score of 85 or above (iii) a CGI score of 1 and (iv) the participant no longer meets Oxford criteria for CFS, CDC criteria for CFS or the London criteria for ME”.***

It is notable that the published paper reports on no such outcome - despite the collection of data that would allow for this measure of “recovery” to have been

calculated. Neither is an alternative measure of “recovery” reported. However, the associated Comment by Bleijenberg and Knoop published in The Lancet is highly misleading on this point.

Despite the absence of any reference to “recovery” in the PACE trial report, Bleijenberg and Knoop lean heavily on this concept, stating:

*"PACE used a strict criterion for recovery: a score on both fatigue and physical function within the range of the mean plus (or minus) one standard deviation of a healthy person's score. In accordance with this criterion, the recovery rate of cognitive behaviour therapy and graded exercise therapy was about 30%"*

This is wrong. As discussed above, White et al do not report the number of participants who “recovered”, despite the stated intention to do so, according to a specific definition as presented in the Trial Protocol.

They do report the number of participants who they describe as having “normal” levels of fatigue and physical function at the end of the trial at 30% and 28%, respectively, of participants who received CBT and GET, so it may be this group that Bleijenberg and Knoop are referring to. However, for the reasons discussed above, “normal” as defined in this context cannot reasonably be described as a state of recovery.

Furthermore, Bleijenberg and Knoop misreport White's definition of “normal” fatigue. They say that the definition represents the mean plus one standard deviation of a healthy person's score. This is not correct as the figure is based instead on the scores of adults attending primary care which, by definition, is a group with a higher rate of health problems than the average healthy person.

The use of this patient group for comparison inflates the number of participants who can be described as having “normal” fatigue.

Readers of the Bleijenberg and Knoop Comment are misinformed that 30% of participants who had CBT or GET recovered, and The Lancet has an urgent duty to correct this misinformation.

## 11. **OVERVIEW OF REPORTING OF RESULTS**

The authors of The Lancet article have presented their selected data with such complexity that it can be construed as their attempt to hide the fact that the PACE Trial results were abysmal.

One can only conclude that Professor White endeavoured to disguise the reality in the wealth of data presented, because the detail in the published figures serves to obscure the fact that the reported “improvements” are miniscule.

This complaint has focused on the primary outcome measures, but results on other measures were similarly under-whelming:

- On the participant-rated CGI (clinical global impression) of change in overall health, 60% of the GET group reported negative or minimal change after 52 weeks and 58% of the CBT group reported negative or minimal change after 52 weeks
- Comparing the baseline score with the score at 52 weeks, on the Work and Social Adjustment scale (rated 0 – 40), people in the CBT group reported a mere 6.4 point change (equating to an adjusted 3.6 improvement over the SMC group who received no treatment) and those in the GET group reported only a 6.8 point improvement (equating to an adjusted 3.2 point improvement over the SMC group).

However, clinging to their firm pre-existing commitment to the CBT and GET interventions offered in the PACE Trial, the authors stated:

***“Our finding that studied treatments were only moderately effective also suggests research into more effective treatments is needed”.***

In the light of the considerations highlighted here, it may be that to describe such results as indicating that CBT and GET are “*moderately effective*” is highly questionable.

No such moderation was shown in the presentation of the findings to the press via the Science Media Centre.

## **12. ANNOUNCEMENT OF RESULTS TO PRESS AT THE SCIENCE MEDIA CENTRE**

On 17<sup>th</sup> February 2011 a press conference was held at the Science Media Centre (SMC) where, as noted in the introduction, Professor Simon Wessely is on the Science Advisory Panel.

The emanations from the Science Media Centre are generally accepted by informed observers to be suspect because it represents only one narrow section of the scientific community: <http://ngin.tripod.com/020602c.htm>

To a not inconsiderable fanfare, the PACE Trial article in The Lancet was launched as being “moderately” successful but only for those patients whose main symptom was “fatigue” (thereby ruling out those with classic ME/CFS).

As detailed above, even this claim is open to question.

However, other statements made were far less measured, and were a cause for very serious concern in terms of their potential to bring about significant adverse consequences to people with ME/CFS. (Even although many people with classic ME

do not experience ‘fatigue’ as their main symptom, this point is routinely disregarded in health care policy and practice.)

The Science Media Centre garnered and publicised the opinions of clinicians known for their adherence to the behavioural model, including some physicians – such as Dr Alastair Miller and Dr Brian John Angus (see below) – who were involved in the PACE trial itself. A number of grossly inflated and quite unjustified claims were made, which, should they go unchallenged, can and will lead to enormously detrimental consequences. For example, the Science Media Centre Press Release included the following:

- Dr Alastair Miller from Liverpool: ***“This trial represents the highest grade of clinical evidence – a large randomised clinical trial, carefully designed, rigorously conducted and scrupulously analysed and reported. It provides convincing evidence that GET and CBT are safe and effective and should be widely available for our patients with CFS/ME”.***

It should be noted that Dr Miller was one of the three “independent” assessors of trial safety data for the PACE Trial.

As the PACE Trial was not a controlled trial, Dr Miller was in error to refer to it as ***“the highest grade of clinical evidence”***, and it cannot be described in such terms.

- Dr Brian John Angus: ***“The study should reassure patients that there is an evidence based treatment that can help them to get better.... It was extremely rigorous... (and) was carefully conducted....As a trial this involved a huge amount of checking and cross checking....This should mean that GET and CBT should be widely available throughout the country....The trial was conducted to a high ethical standard... .It was rigorously performed”.***

Dr Angus was Centre Lead for the PACE Trial in Oxford.

- Professor Derick Wade from Oxford: ***“The trial design of this study was very good, and means the conclusions drawn can be drawn with confidence. This is a very significant finding. It identifies that one commonly used intervention (by which he meant pacing) is not effective (and therefore should not be used), and it confirms the effectiveness of two treatments, and their safety. The study suggests that everyone with the condition should be offered the treatment, and every patient who wishes to be helped should be willing to try one or both of the treatments”.***

The implication of this is that if people refuse to take part in these “rehabilitation” programmes, they do not wish to get better, so they can expect their State benefits to be withdrawn. Professor Wade has notably written to the DWP advising that, despite the WHO classification, ME/CFS is not a neurological disorder but a ***“non-medical illness”*** (letter dated 22<sup>nd</sup> August 2005 to Dr Roger Thomas, Senior Medical Policy Advisor in the Benefit Strategy Directorate at the DWP). He has also written to an ME/CFS patient:

*“it is wrong to fit ME/CFS into a biomedical model of illness”* (letter dated 7<sup>th</sup> July 2006).

- Dr Willie Hamilton: *“This study matters. It matters a lot....It sends a powerful message to PCTs – and the soon-to-be-formed GP consortia – that they must fund CBT or GET. NICE proposed this before the study came out – the evidence is stronger now”*.

Dr Hamilton is Chief Medical Officer for three permanent health insurance companies -- Exeter Friendly Society, Liverpool Victoria and Friends Provident – and he categorises ME/CFS as a functional disorder. (People diagnosed as having this disorder will thus be excluded from payments under a permanent health insurance policy with these companies, since psychiatric disorders are not covered). He was a member of the NICE CG53 Guideline Development Group which recommended CBT/GET as the only intervention for people with ME/CFS.

Thus the Science Media Centre has obtained quotations only from people with known and indisputable biases.

Consideration of the data dispels the assertions quoted above, so it is essential for the protection of vulnerable patients that a more balanced interpretation of the PACE Trial findings is supplied to the media and thus enters the public domain.

As Professor Leonard Jason from the US has pointed out, **the PACE results as published are invalidating the experiences of thousands of patients and Jason has stated on the record that he is worried that as a result of The Lancet article, doctors will push their patients to perform activities that will be harmful** (<http://www.myhealthnewsdaily.com/chronic-fatigue-syndrome-therapies-effective-safe-110217/1187/>).

### 13. SUMMARY / CONCLUSION

When the authors state: *“The PACE findings can be generalised to patients who also meet alternative diagnostic criteria for chronic fatigue syndrome and myalgic encephalomyelitis”*, they are wrong.

The authors, as noted above, are referring only to the *“alternative diagnostic criteria”* used by themselves in the PACE Trial, not to internationally accepted criteria for ME/CFS such as the Canadian Guidelines.

Furthermore, these *“alternative criteria”* were applied to the PACE Trial cohort only when participants had been selected on the basis of the overly-broad Oxford “fatigue” criteria.

The PACE participants were initially screened for eligibility and only those deemed suitable by the PACE trial Investigators went on for further screening. The Invitation

to join the PACE Trial leaflet states: *“You must be diagnosed by us as having CFS/ME. Fatigue or lack of energy must be your main problem”*.

This description complies with the Oxford entry criteria used to recruit participants to the PACE trial but does not fit well with the clinical identity of ME/CFS.

It is notable that in a trial purporting to be studying ME/CFS and despite apparently screening for psychiatric disorders, the authors reported a 47% prevalence of mood and anxiety disorders at baseline, with a near equivalent use of antidepressants (41%).

A 47% prevalence of mood and anxiety disorders is not compatible with results published by others. Research has found that rates of depression in ME/CFS are no higher than in other chronic medical conditions (Shanks MF et al; Brit J Psychiat 1995:166:798-801) and that the rates of overall psychiatric disorders are no higher than general community estimates (Hickie I et al; Brit J Psychiat 1990:156:534-540). Such figures in the PACE Trial cohort confirm inherent problems with the chosen entry criteria (the Oxford criteria), which specifically include those suffering from affective disorders.

Furthermore, it is notable that out of the 3,158 patients screened for eligibility, 1,874 (59%) were excluded because they did not meet the trial’s primary eligibility criteria, including over a thousand patients (1,078; 34%) who did not fit the Oxford entry criteria. That is a very substantial proportion of the referred patients.

Curiously, having completed the initial screening process, doctors refused to permit 46 of the remaining participants to go forward for randomisation into different arms of the trial, but no explanation is provided for doctors declining to allow these patients to participate.

Among the 1,284 potential participants remaining, 554 (43%) declined to participate.

In short, the non-representative nature of the cohort studied means the results apply only to individuals who chose, and were allowed, to participate in the trial itself – so cannot safely be generalised.

However, as a direct result of The Lancet article, it is inevitable that patients with classic ME/CFS will be forced into exercise regimes on pain of losing their State benefits, which are often their only means of financial survival.

The number of obvious flaws in The Lancet article is extraordinary. There are discrepancies, distractions, and omissions in the presentation of data.

The accompanying Comment is highly subjective and factually incorrect.

For those who know the background to the PACE Trial, the article cannot be taken at face value. The study question was irrelevant; the study itself did not add anything new; its entry criteria were inappropriate for the population supposedly being studied and to whom the results will be generalised (ie. people with ME/CFS, who are clinically different from the ambulant fatigued patients used in the trial such as, for example, those known to be suffering from post-herpetic fatigue); there was no active

control group such as relaxation as has occurred in other trials; the most important source of bias was not avoided; the study was not performed according to the original protocol, to which there were numerous major (not the customary minor) amendments; the statistical analyses appear to be contorted (to say the least); the use of an objective outcome measure of activity (actometers) was abandoned during the trial with no credible explanation; the published data do not justify the authors' and commentators' conclusions; key data remain unpublished, and there were serious conflicts of interest, for all of which The Lancet might wish to seek explanation from the authors of the article.

The Investigators ignored the extensive biomedical research literature and mis-portrayed ME/CFS as a dysfunctional belief instead of a complex multi-system neuroimmune disease. Even though they acknowledge they do not know what causes "CFS/ME", in the CBT and GET arms of the trial the PIs assumed that participants had no physical disease but did not inform participants of this and portrayed their own assumptions as established facts, which is misleading and scientifically untenable. That meant that patients were unable to give fully informed consent as required for a clinical trial

**If the Wessely School's "cognitive behavioural" model of ME/CFS were correct, then participants should recover once they regain their physical strength and overcome their alleged kinesiophobia, since the model posits that the symptoms of ME/CFS result not from organic pathology (CBT Therapists' Manual, page 16) but from reversible physiological changes secondary to inactivity. This clearly did not happen.**

Critical analysis of the data presented in The Lancet article strongly suggests that the recorded outcomes of the PACE trial undermine the supposed "evidence-base" that underpins the NICE Clinical Guideline 53 (see below).

Despite this, it seems that Professor White's own fixed illness beliefs cannot be changed. On 12<sup>th</sup> March 2011, the following was posted on various ME internet forums:

*"I had a visit from my Occupational Therapist on the ME team. She has spoken directly to Peter White via the Yahoo site for ME NHS workers.*

*"There is immense disquiet amongst the OTs on the ME teams who deliver the care within the UK about PACE, especially the fact that PACE did not test ... pacing...but instead used Adaptive pacing..."*

*"She tells me Peter White is adamant that PACE results were crystal clear and would direct the way future funding is granted.*

*"ME NHS staff are also aware that the patients tested were probably in the main not suffering from ME, but they are, in my opinion, very wary about losing their jobs and too frightened to speak openly in the press.*

*"My OT was the first to criticise the trial via their own website...and Peter White answered almost immediately and with forthright language. Intimidation?"*

***“My OT assured me... that professionals in the front line would not change how they approach this illness.***

***“She knows we are ill and ...she is very frustrated.***

***“Peter White is so blinkered and desperate to keep a hold on his powerbase....”.***

This is further evidence of the realisation by NHS staff at grass roots level that the dogma of the Wessely School about ME/CFS does not work in practice.

In summary, the authors have struggled to seek material differences in what can only be described as poor results in all sections because, overall, there is little or no clinically effective outcome.

Prior to the PACE results being published, the MRC conceded in writing about CBT/GET that: ***“there was a lack of high quality evidence to inform treatment of CFS/ME and in particular on the need to evaluate treatments that were already in use and for which there was insufficiently strong evidence from random controlled trials of their effectiveness”*** (personal communication from Dr Frances Rawle, Head of Corporate Governance and Policy, 6<sup>th</sup> January 2011).

That is a astonishing admission, since the NICE Clinical Guideline 53 of 22<sup>nd</sup> August 2007 relied upon the pre-PACE Trial Wessely School “evidence-base” to recommend the use of CBT and GET nationally as the intervention of choice for ME/CFS, yet the MRC has confirmed – in writing -- that there was insufficient evidence for the implementation of this nationwide programme of CBT and GET recommended by NICE in its Clinical Guideline 53.

Now that the PACE results are finally published, there is still a resounding ***“lack of high quality evidence”*** and ***“insufficiently strong evidence”*** of the efficacy of CBT/GET for people with ME/CFS.

NICE, however, announced on 14<sup>th</sup> March 2011 that there will be no review of CG53 until 2013: even though some stakeholders requested a review on the grounds that the interventions recommended in CG53 should be driven by the scientific biomedical evidence (ie. not the Wessely School’s assumptions of reversibility with cognitive restructuring), NICE remained intransigent:

***“...interventions recommended in the original guideline, such as CBT and GET, were described as the interventions for which there is the clearest evidence-base of benefit. This is supported by the recently published PACE trial....The results of the study are in line with current NICE guideline recommendations on the management of CFS/ME....There are no factors...which would invalidate or change the direction of the current guideline recommendations. The CFS/ME guideline should not be updated at this time”.***

Because of the Wessely School’s non-science-based determination to regard ME/CFS as a functional disorder, and because the PIs and others involved with the PACE Trial have been so successful in disregarding not only the WHO’s classification of ME/CFS

as a neurological disorder but also the biomedical evidence-base of over 4,000 published papers -- to the advantage of the insurance industry and the DWP -- they have successfully steered their projects through ethics committees and funding boards but have produced nothing but pseudo-science.

Recently, a senior UK medical doctor who has a close family member affected by ME/CFS wrote referring to *“closed minds in the UK”* and he said: *“Unfortunately, we were anticipating that the published results would be flawed because of the key people behind the trial”* (personal communication, 28<sup>th</sup> February 2011).

That observation sums up the current situation in the UK; the Wessely School do indeed have closed minds about ME/CFS.

Given the results of trials of the same interventions as those used in the PACE Trial which came to very different conclusions (for example: Health-related quality of life in patients with chronic fatigue syndrome: group cognitive behavioural therapy and graded exercise versus usual treatment. A randomised controlled trial with 1 year of follow-up. M Nunez et al. Clin Rheumatol doi 10.1007/s10067-010-1677-y), for the Lancet to have published the White et al paper, which signally fails to place the research in appropriate context by citing such papers, calls into serious question the journal’s knowledge of and editorial policy about ME/CFS.

In the light of this (and many known other) complaints, The Lancet should retract the article reporting the contrived results of a clinical trial which failed to mention the biomedical evidence that invalidates the premise upon which the study was based and, moreover, was a study designed not to legitimise the disabling symptoms resulting from a serious neuroimmune disorder but to re-structure participants’ correct cognitions into believing that they do not suffer from an organic disorder, merely from aberrant beliefs and deconditioning.

As the charity Invest in ME stated in its initial statement about The Lancet article: *“The purpose of any medical research should be the benefit of the patients and the PACE trials do not benefit ME patients but rather the known vested interests who control what the media publish and what the Medical Research Council fund in relation to ME/CFS....By any measure the PACE trials are flawed and are not the result of proper research. Using diagnostic criteria which do not define patients with ME/CFS and which exclude people with neurological disorders means that patients participating in these trials were of a heterogeneous variety – thus making the result completely irrelevant. This nullifies all of this study. The PACE trials are designed, created and performed by those who view ME/CFS as a consequence of wrong illness beliefs or deconditioning. The PACE trials are bogus science and have no relevance in the treatment of people suffering from myalgic encephalomyelitis”* (Co-Cure 18<sup>th</sup> February 2011).

On 1<sup>st</sup> March 2011 the Whittemore Peterson Institute for Neuroimmune Disorders commented about The Lancet article: *“...it is irresponsible to suggest these methods (CBT/GET) would be effective for patients with ME and CFS. In addition, research physiologists have shown that patients suffer from relapses of their illness when forced to exercise against their will or when told to ‘push through’ their illness. Since the WPI’s discovery of the high correlation of a retroviral infection,*

*with those who suffer from neuroimmune diseases, it is even more important that physicians do not harm their patients psychologically by suggesting they are responsible for, or can be talked out of, their illness”* (UK PACE Trials: When Misguided Doctors Can Do More Harm Than Good: [http://www.wpinstitute.org/news/docs/WPI\\_PaceTrials\\_030111.pdf](http://www.wpinstitute.org/news/docs/WPI_PaceTrials_030111.pdf)).

On 5<sup>th</sup> March 2011 the charity Action for ME issued a Policy Group strategy in response to the PACE results published in The Lancet and it noted the *“exaggerated interpretation of statistical data on therapeutic effectiveness and safety.... There is a growing body of comment that reinforces our stance that the PACE trial findings have been exaggerated.... We anticipate a risk that DWP guidelines as well as NICE Guideline 53 could be revised inappropriately through poor understanding of the PACE trial results”* (<http://www.afme.org.uk/news.asp?newsid=1069>).

To the detriment of people with ME/CFS, NICE has already made its position clear.

In his submission about the (then draft) NICE Guideline (24<sup>th</sup> November 2006, comments on chapter 6, page 308), Professor White was unambiguous: *“These goals should include recovery, not just exercise and activity goals. If it takes “years” to achieve goals, then either the goals are wrong or the therapy is wrong. What other treatment in medicine would take years to work?”*

In the light of the accumulated biomedical evidence stretching over many years, what further evidence does Professor White require before acknowledging that he is wrong-headed and that the somatoform approach to ME/CFS is without foundation?

If the UK health service is driven by evidence-based medicine and economic prudence, it must urgently start dealing with biomedical science and abandon its irresponsible infatuation with the erroneous concept of ME/CFS as a somatoform disorder and its acceptance of the continued conflation of a neuroimmune disorder with medically unexplained chronic fatigue.

By letter dated 6<sup>th</sup> January 2011, Dr Frances Rawle, Head of Corporate Governance and Policy at the MRC wrote in a personal communication:

*“Whether the money for the trial proves to have been well spent will of course depend on the outcome of the trial....a lack of effectiveness for any of these treatments would not necessarily mean that the money spent had been wasted, as redirection of NHS resources currently used for interventions shown to be ineffective would be a worthwhile outcome for a trial....If, as you clearly believe, the treatments being evaluated are either ineffective or positively harmful, the results of the trial will likely show this. This in itself would be a valuable outcome of the trial, in that it would be evidence to support the redirection of NHS resources away from ineffective therapy”*.

Despite both the failure of the FINE Trial and the “modest” results from the PACE Trial, and despite the MRC’s letter, Professor White is already urging yet more “research” to prove the efficacy of CBT and GET in ME/CFS and asserting that the results of the PACE Trial *“will direct the way future funding is granted”*.

Any such “*future funding*” would defy the military maxim: “Never reinforce failure”.

The PACE study has failed to achieve any of the Wessely School’s goals or targets. No further public funding can possibly be justified.

The Lancet is responsible for publishing an unscientific, misleading and contrived article, prompt retraction of which is necessary, not only to prevent yet more iatrogenic harm to patients, but also to prevent further massive waste of tax-payers’ money by yet more unquestioning endorsement of Professor White’s disproven beliefs.

## APPENDIX 1

### The published views about ME/CFS of those involved with the PACE Trial

The Chief Principal Investigator, Professor Peter White does not accept that ME/CFS is an organic disease and asserts that it is an “abnormal illness belief”.

He believes that in general, *“medicine is currently travelling up a ‘blind alley’ (and) this ‘blind alley’ is the biomedical approach to healthcare. The biomedical model assumes that ill-health and disability is directly caused by diseases and their pathological processes (but) there is an alternative approach -- the biopsychosocial approach is one that incorporates thoughts, feelings, behaviour, their social context and their interactions with pathophysiology”* (Biopsychosocial Medicine: An integrated approach to understanding illness edited by Peter White; OUP 2005).

Many people believe it is a retrograde step to reject the hard-earned scientific evidence gained over centuries that ill-health is directly caused by disease and its pathological processes; further, they reject the notion that the correct approach to healthcare should be primarily the psychosocial one, in which “aberrant” thoughts, feelings and behaviour can supposedly be “modified” by the Wessely School’s own brand of cognitive restructuring with graded aerobic exercise (CBT/GET), resulting in restoration of health and in economic productivity for the State.

In a major medical textbook (Clinical Medicine: Kumar and Clark, 5<sup>th</sup> edition), together with the late Professor Anthony Clare, Peter White contributed the section on Psychological Medicine. The entry for Myalgic Encephalomyelitis directs the reader to the entry for CFS, which in turn directs the reader to Section 21 (Psychological Medicine) where CFS/ME is listed under “Functional or Psychosomatic Disorders: Medically Unexplained Symptoms” and White asserts that the psychiatric classification of these disorders is “*somatoform disorder*”, which he states were previously known as “*‘all in the mind’, imaginary and malingering*”.

Principal Investigator Professor Michael Sharpe’s published views about ME/CFS include the following:

*“The label of CFS avoids the connotations of pseudo-disease diagnoses such as ME”* (Occup Med 1997;47:4:217-227).

*“Those who cannot be fitted into a scheme of objective bodily illness yet refuse to be placed into and accept the stigma of mental illness remain the undeserving sick of our society and our health service”* (ME. What do we know (real physical illness or all in the mind?))” (Lecture given in October 1999 by Michael Sharpe, hosted by the University of Strathclyde).

*“My own view has long been that the issues around CFS/ME are the same as those surrounding the acceptance and management of (patients) who suffer conditions*

*that are not dignified by the presence of what we call disease”* (Journal of Psychosomatic Research 2002:52:6:437-438).

In his inaugural lecture for his Personal Chair in Psychological Medicine and Symptoms Research (The Science of the Art of Medicine, University of Edinburgh, 12<sup>th</sup> May 2005), Professor Sharpe spoke on “*functional medicine*” and on how to treat diseases with “*no pathology*” such as ME/CFS, an insupportable assertion, given the extensive evidence-base of serious pathology shown to exist in ME/CFS.

Professor Sharpe is a member of the DSM-5 study group that is redefining somatoform disorders, with the creation of a new category of “Complex Somatic Symptom Disorder” (CSSD). The existing evidence suggests that the DSM Somatic Symptom Disorder Work Group intends to ensure that ME/CFS will fall within the purview of the new category of CSSD because Sharpe et al believe ME/CFS to be an example of a CSSD (ie. they believe that ME/CFS patients complain of physical symptoms that do not result from underlying physical disease but are the consequence of abnormal illness beliefs, and that the abnormal beliefs are responsible for the perpetuation of the perceived disability).

Principal Investigator **Professor Trudie Chalder’s** beliefs about “CFS/ME” are unambiguous: in 2007 the Institute of Psychiatry funded a project called “Emotional Processing in Psychosomatic Disorders”. The Section of General Hospital Psychiatry at the IoP advertised for a psychology graduate to work on the project, which would “*involve working across the Section on Eating Disorders and the Chronic Fatigue Research and Treatment Unit*”. The job reference was 07/R68. The advertisement said: “*The post holder will work under the immediate supervision of Professors Ulrike Schmidt (AN) and Trudie Chalder (CFS)*”.

The study literature stated: “*The comparison with CFS will allow (researchers) to gauge whether any social cognition deficits are unique to anorexia, or reflect more global symptoms of psychiatric illness with marked physical symptoms*”. Thus, according to one of the MRC PACE Trial Principal Investigators, “CFS” is “*a psychiatric illness with marked physical symptoms*”. Applicants were informed that: “*Anorexia Nervosa (AN) and chronic fatigue syndrome (CFS) are classical psychosomatic disorders where response to social threat is expressed somatically*”.

Although not a Principal Investigator, psychiatrist **Professor Simon Wessely** was Director of the PACE Clinical Trial Unit and directed the centre statistician.

In the late 1980s, Wessely was involved with an organisation now called HealthWatch (which used to be called The Campaign Against Health Fraud). In its own literature, the Campaign stated that its aims were “*to oppose...unnecessary treatment for non-existent diseases*”. Wessely was listed as a “*leading member of the campaign*” and it is the case that he asserts ME is a “*non-existent disease*”.

In February – April 2002, the BMJ ran a poll of what readers considered “non-diseases” in which Wessely was instrumental; it concluded that ME, along with big

ears and freckles, was a “non-disease” that is best left medically untreated (BMJ 2002;324:883-885).

Wessely is renowned for his deeply-held belief that ME does not exist; he believes that ME is a behavioural disorder and that patients’ ascription of the disease to a virus is “*somatisation par excellence*” (J Psychosom Res 1994;38:2:89-98).

Professor Wessely’s published views about ME/CFS patients include the following:

***“The description given by a leading gastroenterologist at the Mayo Clinic remains accurate: ‘The average doctor will see they are neurotic and he will often be disgusted with them’ ”*** (Chronic Fatigue and Myalgia Syndromes. In: Psychological Disorders in General Medical Settings Ed: N Sartorius et al. Pub: Hogrefe & Huber, 1990).

In 1992, Professor (then Dr) Simon Wessely’s stated intention was to “eradicate” ME: ***“It seems that ME sufferers prefer to feel that they have a ‘real’ disease – it is better for their self-esteem (and) the label ‘ME’ helps legitimise their dealings with doctors”***. Referring to a programme of graded exercise for ME patients, he said there were ***“a very large number of drop-outs from treatment, largely related to the fear these patients had, albeit inappropriately, of accepting that their disorder was ‘all in the mind’ ”***. Nothing could be clearer: the conference report records that Wessely stated that ME patients’ fear of accepting that their disorder was ‘all in the mind’ was ‘inappropriate’, indicating that he considers that it is “all in the mind” (Eradicating myalgic encephalomyelitis (ME)). Simon Wessely. Report of meeting held on 15 April 1992 at Belfast Castle; Pfizer Invicta Pharmaceuticals, p4-5).

***“The inclusion (in ICD-10) of benign myalgic encephalomyelitis as a synonym for postviral fatigue under Diseases of the Nervous System seems to represent an important moral victory for self-help groups in the UK...Neurasthenia remains in the Mental and Behavioural Disorders chapter under Other Neurotic Disorders...Neurasthenia would readily suffice for ME”*** (Lancet 1993;342:1247-1248).

***“I will argue that ME is simply a belief, the belief that one has an illness called ME.... I will argue that this line here (overhead slide) represents not the line between low and high cortisol responses (but) the line between real and unreal illness”*** (Microbes, Mental Illness, The Media and ME: The Construction of Disease Simon Wessely. 9<sup>th</sup> Eliot Slater Memorial Lecture, Institute of Psychiatry, London, 12 May 1994).

***“The term ME may mislead patients into believing they have a serious and specific pathological process”*** (Chronic Fatigue Syndrome. Report of a Joint Working Group of the Royal Colleges of Physicians, Psychiatrists and General Practitioners October 1996 Simon Wessely, Peter White et al).

***“No investigations should be performed to confirm the diagnosis”*** (ibid).

***“Other symptoms identified in the chronic fatigue syndrome (include) increased symptom-monitoring”*** (Ann Intern Med 2001;134:9S:838-843). In correspondence

arising from this paper, Wessely wrote: ***“I can sleep easy at night when it comes to treatment. I know that we have done more good than harm. All I know is that I am quietly proud of what our group has achieved over the years”.***

***“If sections of the media advocate an exclusively organic model, as has happened with CFS, the biomedical model may become firmly enshrined for patients and families at the expense of psychosocial models”*** (Journal of the Royal Society of Medicine 2003;96:223-227).

***“Functional somatic syndromes...include chronic fatigue syndrome”*** (Rev Bras Psiquiatr. September 2005;27:3: Sao Paulo).

For more illustrations of what Professors Wessely, White and Sharpe have published about people with ME/CFS over the last 25 years, see: [http://www.meactionuk.org.uk/Quotable\\_Quotes\\_Updated.pdf](http://www.meactionuk.org.uk/Quotable_Quotes_Updated.pdf)