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Key Concerns about the PACE trial

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Introduction

Not only has Myalgic Encephalomyelitis (ME, also known as chronic fatigue syndrome or CFS) been classified as a neurological disorder by the WHO since 1969, but on 16th August 1992, the Rt Hon Stephen Dorrell MP, UK Minister of Health, went on public record confirming that: "*ME is established as a medical condition*". The Department of Health officially accepts it as a chronic neurological disorder and since 2003 ME/CFS has been classified in the UK Read Codes used by all GPs as a neurological disease (at F 286). Furthermore, since its inception in March 2005 the UK National Service Framework on chronic neurological conditions includes ME/CFS, and the Department for Work and Pensions has confirmed in writing that it does not consider ME/CFS to be a mental disorder (letter of 21st November 2011 to the Countess of Mar signed by Lord Freud, Minister for Welfare Reform).

It thus cannot be referred to and treated as a behavioural disorder, but that is exactly what happened in the PACE trial.

Professor (now Sir) Simon Wessely directed the management of the PACE trial; he is a psychiatrist who is internationally known for his insistence that ME does not exist other than as an aberrant belief: "*I will argue that ME is simply a belief, the belief that one has an illness called ME"* (9th Eliot Slater Lecture, IoP, 12th May 1994). He disagrees with the WHO's classification and in defiance of the significant international evidence-base of organic pathology, he and his close colleagues have strived for over two decades to reverse the WHO classification of ME from neurological to psychiatric.

It was as long ago as 2000 that Anthony Komaroff, Professor of Medicine at Harvard and a world leader in ME/CFS, summarised in The American Journal of Medicine the key areas in which ME/CFS differs from psychiatric illness:

"Objective biological abnormalities have been found significantly more often in patients with (ME/CFS) than in the comparison groups. The evidence indicates pathology of the central nervous system and immune system. Autonomic nervous system testing has revealed abnormalities of the sympathetic and parasympathetic systems that are not explained by depression or physical deconditioning. Studies of hypothalamic and pituitary function have revealed neuroendocrine abnormalities not seen in healthy control subjects. There is considerable evidence of a state of chronic

immune activation. ***In summary, there is now considerable evidence of an underlying biological process which is inconsistent with the hypothesis that (ME/CFS) involves symptoms that are only imagined or amplified because of underlying psychiatric distress. It is time to put that hypothesis to rest****"* (The Biology of the Chronic Fatigue Syndrome. Am J Med 2000:108:99-105).

Even earlier, in 1994, one of the world's most renowned ME/CFS clinicians, Dr Daniel L Peterson from the US, went on record: *"****In my experience, it is one of the most disabling diseases that I care for, far exceeding HIV disease except for the terminal stages****"* (Introduction to Research and Clinical Conference, Fort Lauderdale, Florida, October 1994; published in JCFS 1995:1:3-4:123-125).

In 1995, Professor Mark Loveless, Head of the AIDS and ME/CFS Clinic at Oregon Health Sciences University said in his Congressional Briefing that an ME/CFS patient: ***"feels effectively the same every day as an AIDS patient feels two weeks before death; the only difference is that the symptoms can go on for never-ending decades"****.*

In 2004, Dr William Reeves, Chief of the ME/CFS research programme at the US Centres for Disease Control, (CDC) reported that ME/CFS patients *"****are more sick and have greater disability than patients with chronic obstructive lung or cardiac disease, and that psychological factors played no role****"* (Press Release, AACFS, 7th October 2004).

Also in 2004, a randomised clinical trial found *"****In comparison with other chronic illnesses such as multiple sclerosis, end-stage renal disease and heart disease, patients with (ME)CFS show markedly higher levels of disability****" (Am J Occup Ther 2004:58:35-43).*

On 15th October 2009, Professor Nancy Klimas, then Professor of Medicine, Microbiology and Immunology at the University of Miami, famously said in the New York Times*: "****I hope you are not saying that (ME)CFS patients are not as ill as HIV patients. I split my clinical time between the two illnesses, and I can tell you that if I had to choose between the two illnesses I would rather have HIV****"*.

None of this cuts any ice with the Wessely School and its members have long waged war against people with ME/CFS.

In 1990 Wessely wrote that ME exists *"only because well-meaning doctors have not learnt to deal effectively with suggestible patients"* (Psychological Medicine 1990:20:35-53); in 1991 he cited comments made by doctors between 1880 and 1908 on patients with neurasthenia, with the very clear implication that such descriptions apply equally well to current ME patients: *"always ailing, seldom ill; a useless obnoxious element of society; purely mental cases; laziness, weakness of mind and supersensitiveness characterises them all; the terror of the busy physician"* (BMB 1991:47:4:919-941); in 1992 the Wessely School gave directions that in ME/CFS, the first duty of the doctor is to avoid legitimisation of symptoms (MRC

Summary of CIBA Foundation Symposium on CFS, May 1992: ref: S 1528/1); in 1996 recommendations were made by Wessely et al in a Joint Royal Colleges Report (CR54) that no investigations should be performed to confirm the diagnosis and in 1999, Professor Michael Sharpe said in a lecture at Strathclyde University: *"Purchasers and Health Care providers with hard pressed budgets are understandably reluctant to spend money on patients…for whom there is controversy about the 'reality' of their condition (and who) are in this sense undeserving of treatment…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."*

In October 2003, in a frenzied attack on people with ME and on those scientists and clinicians who regard it as an organic disorder, Wessely asserted that those who disagree with him and believe ME to be an organic disorder (to whom he referred as *"the radicals"*) are *"crazy"* and that they are *"engaged in fantasies, lies and gross distortions".* He wrote that the *"radicals"* are left *"fighting yesterday's battles"* (seemingly because he believes he has established that ME does not exist except as a false illness belief), that they need a *"reality check"* and that *"their behaviour is outrageous"* (private communication; available to Medical Defence Union lawyers on request).

Wessely's dismissal of the biomedical evidence on ME/CFS has continued unabated, even though there is substantial evidence of pathology affecting the central and autonomic nervous systems, the immune system and the cardiovascular, endocrine, gastro-intestinal and musculoskeletal systems. Coroners' reports confirm that people die from ME/CFS and published evidence shows that people with ME/CFS die 20 years prematurely.

At a medical meeting in March 2013 held in Bristol, Wessely informed attendees that ME has been caused almost entirely by the *"shockingly"* negative way in which some ME charities, in particular the ME Association, portray it as a viral illness, saying that this has harmed patients as it encourages them to focus too much on symptoms and to be fearful of activity, resulting in a vicious cycle of deconditioning. Making no distinction between chronic "fatigue" and ME/CFS, doctors were informed by Wessely that all patients with CFS would benefit from the same management regime, namely behavioural therapy and exercise (Research in Chronic Fatigue Syndrome – ups and downs; Bristol Medico-Chirurgical Society; 13th March 2013: approved for Continuing Medical Education).

Professor Wessely was intrinsically involved with the PACE trial and the three Principal Investigators (Professor Peter White, Michael Sharpe and Trudie Chalder) all work for the permanent health insurance industry.

<u>Key areas of concern about the PACE Trial</u>

After some years of unsuccessful attempts by Wessely's close colleague, psychiatrist Professor Peter White (Chief Principal Investigator), the PACE trial started in 2004 and cost UK taxpayers £5 million. "PACE" is the acronym for **P**acing, **A**ctivity, and **C**ognitive behavioural therapy, a randomised **E**valuation, interventions that, according to one of the Principal Investigators, are without theoretical foundation.

The PACE trial was predicated on the Investigators' belief that patients with ME/CFS must restructure their thought processes so that they no longer think they are physically sick; this was to be achieved by directive (as opposed to supportive) cognitive behavioural therapy (CBT, based on the illness model of fear avoidance) and by incremental aerobic graded exercise therapy (GET, based on the illness model of both deconditioning and exercise avoidance). No mention whatsoever was made of the well-documented underlying biomedical pathophysiology.

Both the Department for Work and Pensions (DWP) and the insurance industry took a keen interest in the PACE trial. It was the only clinical trial ever funded by the DWP and it did so because its then Chief Medical Advisor, Dr (now Professor Sir) Mansel Aylward, who works closely with the insurance industry, was assured by Professor White (who was lead advisor to the DWP on CFS) that it would remove people with ME/CFS from claiming benefits. This was effectively confirmed by the MRC by letter on 17th March 2011. In 2002 a book entitled "Work and Mental Health: An Employers' Guide" was published by the Royal College of Psychiatrists Publications; it was co-edited by Dr Maurice Lipsedge, a psychiatrist who, like Professor Michael Sharpe, worked for the insurance industry. The book was sponsored by the massive re-insurance company Swiss Re (UK) plc for which Professor Peter White was Chief Medical Officer. In his contributed chapter, Professor Sharpe stated about ME/CFS:

"Prognosis is worse for patients who have a conviction that the cause is purely 'physical'….CBT places particular emphasis on helping patients to reappraise their illness beliefs…..Refusal to accept appropriate treatment by the National Health Service and misleading advice are common problems".

Reappraising participants' illness beliefs by means of "cognitive restructuring" (aka "brain washing") was the ethos of the PACE trial.

The PACE trial is believed to be the first and only clinical trial that patients and the charities which support them tried to stop before a single patient could be recruited. **This was because the premise upon which the trial was predicated (the Investigators' belief that ME/CFS is perpetuated by psychological and behavioural factors and by faulty cognitions, activity avoidance and "*hypervigilance to normal bodily sensations*") had already been invalidated by the considerable body of evidence-based biomedical research on ME/CFS, hence the PACE trial should never have taken place.**

To international consternation, the Medical Research Council allowed the PACE trial to proceed as if this substantive body of mainstream knowledge did not exist, which was intellectually dishonest: a key principle of clinical research on human

subjects is that it should build on foundations of existing knowledge about the disorder being studied, but in the case of the PACE trial, the biomedical evidence-base was simply air-brushed out of existence by the Investigators and those who supported them.

Specific concerns

Detailed analyses of the many failings of the PACE trial -- with full references -- can be found at http://www.meactionuk.org.uk/magical-medicine.htm and at http://www.meactionuk.org.uk/COMPLAINT-to-Lancet-re-PACE.htm and at http://www.meactionuk.org.uk/Normal-fatigue.htm and at www.investinme.org/Article435StatisticsandME.htm

Failure to fully declare competing interests

Although some of the Principal Investigators' (PIs) competing interests were briefly mentioned in The Lancet article when selective results of the PACE trial were published in February 2011, trial participants were not initially made aware of the substantial competing financial interests of all three Principal Investigators (ie. their work for the insurance industry and for the DWP which co-funded the trial).

As well as being Chief Medical Officer for Swiss Re, the Chief Principal Investigator, Professor Peter White, was also Chief Medical Officer for Scottish Provident, an insurance company with a record of not paying legitimate permanent health insurance (PHI) claims to those with ME.

The insurance companies known to be involved in ME/CFS claims include UNUM, Swiss Life, Canada Life, Norwich Union (now Aviva), Allied Dunbar, Sun Alliance, Skandia, Zurich Life and Permanent Insurance, and as re-insurers, the massive Swiss Re (not the same as Swiss Life). These insurance companies all seem to be involved in re-insurance; for example, Norwich Union (now Aviva) uses Swiss Re. There seem to be two ways in which permanent health policies are underwritten between insurers and re-insurers: either the insurers agree to pay claims up to a pre-determined cut-off limit, after which the re-insurer becomes liable, or else the insurer and the re-insurer agree from the outset to share the costs of a claim.

This means that there is little hope of an ME/CFS claimant succeeding in a PHI claim, because both the insurers and the re-insurers inter-refer claimants with ME/CFS to the same psychiatrists, a situation confirmed by written evidence.

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). 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.

Seven years later, nothing has changed and the same group of doctors who work for the insurance industry continue to influence UK policy on ME/CFS.

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), not all of which were declared in The Lancet article.

Professor 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.

Another Principal Investigator in the PACE trial, Professor Michael Sharpe, is also deeply 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). Professor Sharpe is known for his recommendation to insurers that claimants with ME/CFS should be subject to covert video surveillance.

Members of the Scottish Parliament wrote 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. Professor Sharpe asked MSPs to withdraw their statements to Allied Dunbar about him but they refused to do so.

The third Principal Investigator in the PACE trial, Professor Trudie Chalder, is also involved with the insurance industry in far more depth than is apparent from her brief declaration in the "Conflicts of Interest" in The Lancet. 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 17th May 1995 (at which attendees were informed that ME/CFS has been called "*the malingerer's excuse*"), Miss Chalder spoke on *"Management of CFS",* which she said included increasing activity and returning to work, and on "*Selling the treatment to the patient",* whilst Professor Michael Sharpe spoke on "*cognitive psychotherapy"* and Professor Simon Wessely spoke on "*The Facts and the Myths"* about ME/CFS.

A physiotherapist involved with the PACE trial, Jessica Bavinton, is also more deeply involved with the insurance industry that is apparent from her brief declaration in The Lancet; she 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 on CFS (CG53) she declared her intention to publish, an intention which placed her in the position of having a commercial interest in the outcome of the PACE Trial.

Miss Bavinton works for more than three PHI companies, one being Scottish Provident, whose claims handler Kenneth MacMahon by letter dated 7th August 2007 stated 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 13th August 2007, in a (recorded) telephone conversation, Miss Bavinton herself stated that she does *"lots of these assessments for insurance companies"*.

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.

The Chair of the West Midlands Multicentre Research Ethics Committee (MREC) which granted ethical approval for the PACE trial (reference MREC/02/7/89), Dr Jammi Rao, went on record in 2002: "*Consent obtained on the basis of withholding information on an issue that patients consider important is not fully informed consent"* (BMJ 2002:325:36-37).

Failure to fully declare competing interests is in breach of section B22 of the Declaration of Helsinki 2000 (the version in force at the time of the PACE trial).

Failure to comply with professional ethical guidance and Codes of Practice

In the PACE Trial Protocol, the Investigators stated 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 by the Investigators, the provisions of the General Medical Council Guidance Good Practice in Research and Consent to Research would also

have applied, as would 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 to comply with the required ethical standards, for example:

- it appears that the PACE trial did not conform to the Declaration of Helsinki in full: participants and others have confirmed in writing that coercion was used to compel people to enter the trial on threat of losing medical support for their State benefits (breaching A8 and B20); furthermore, coercion was said by participants to have been used to prevent them from withdrawing from the trial, and participants have provided written evidence of this

- medical research involving human subjects must be based on a thorough knowledge of the existing body of scientific literature, but the Investigators ignored the substantial biomedical evidence-base on ME (breaching B11) and the trial was predicated on the Investigators' firm belief that ME/CFS is not an organic disease but an aberrant illness belief. **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, as happened in the PACE trial?**

- the anticipated benefits of two of the interventions were greatly overplayed to participants in the CBT and GET groups but not to participants in the APT (pacing) or SSMC groups (standardised specialist medical care): those in the former two groups were repeatedly led to believe that they would be cured and could return to work, with therapists even offering to write to participants' employers to ensure that they would be returning to work, whilst those in the APT group received no such guarantee

- despite the Investigators' assurances of the strictest confidentiality, participants' data were not kept securely and were stolen from an unlocked drawer (Southwark police crime incident number 3010018-06 reported on 22nd March 2006); this was in breach of section B21. Affected participants were not made aware that confidential information about them had been stolen

- the Investigators already knew that CBT and GET do not work for ME/CFS patients: "*These interventions are not the answer to CFS*" (Editorial: Simon Wessely; JAMA 19th 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 (breaching B22).

It appears that the Investigators likewise failed to observe necessary principles of good research required by the GMC "Good practice in research and Consent to research" (http://www.gmc-uk.org/static/documents/content/Research_guidance_FINAL.pdf)

For example, the following requirements should have pertained but evidence abounds that they did not:

- 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".*

Written evidence exists of failures by the Investigators in all those domains.

The PACE Trial was jointly funded by the Department of Health, whose own Research Governance Framework for Health and Social Care, Second Edition, 2005, states:

"2.3.1: All existing sources of evidence…must be considered carefully before undertaking research".

Without doubt, the Investigators were in breach of this important tenet of scientific research.

The Governance arrangements for NHS Research Ethics Committees, 2001, state:

"9.8 The Research Governance Framework makes it clear that the sponsor (in this case the main sponsor was Barts and the London, Queen Mary School of Medicine and Dentistry, but ultimate responsibility rested with Professor Peter White) *is responsible for ensuring the quality of the science. Paragraphs 2.3.1 and 2.3.2 state:* ***It is essential that existing sources of evidence, especially systematic reviews, are considered carefully prior to undertaking research. Research which duplicates other work unnecessarily or which is not of sufficient quality to contribute something useful to existing knowledge is in itself unethical".***

As noted above, the Investigators already knew from previous published research that CBT and GET are not the answer to ME/CFS.

Some important concerns relating to the Investigators' failures to comply with the above ethical requirements include the following:

- participants were intentionally misinformed about the nature of ME/CFS; they were informed that their symptoms were not the result of any pathological process and they were disabused of their correct belief that ME/CFS is an organic illness

- 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 implied that participation in the PACE Trial would afford them specialist medical care that was not available elsewhere. This was untrue: 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 does not constitute *"specialist medical care";* furthermore, the SMC arm of the PACE Trial used 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 be considered to be knowledgeable "medical specialists" experienced in the care of people with ME/CFS, so participants were deceived. Furthermore, one of

the "specialist medical care doctors" was named in The Lancet article as being Simon Wessely, who believes that ME does not exist except as an aberrant belief that one has an illness called ME

- participants were seriously misled about one of the arms of the trial, Adaptive Pacing Therapy (APT). They were led to believe they were entering a trial testing the efficacy of pacing; this was untrue, so they may thus not have been in a position to give fully informed consent. All three Principal Investigators are known to be strongly opposed to pacing (BMJ 5th January 2002:324:7; BMJ 19th January 2002:324:131) and the Chief PI, Professor White, has publicly admitted conflicts of interest about it (Postgraduate Medical Journal 2002:78:445-446). For all three PACE trial PIs to have publicly-known conflicts of interest about one of the interventions being tested in the trial and to be strongly opposed to that intervention may cast doubt on the validity of their finding that pacing does not work. It is therefore necessary to be aware that the 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 was a vehicle for incremental aerobic exercise and it involved planning, achieving and sustaining targets. The APT Therapists' Manual listed requirements for APT including ***"plan set activity in advance"*** (so activity had to be ***"set activity",*** not simply what the patient might have been capable of doing at the time)*;* there was to be ***"activity analysis";*** APT participants had to ***"constantly review model, diaries and activity"*** and there was the requirement to ***"involve relatives",*** which is nothing like pacing, ie. "doing what you can when you can". The Lancet article seriously misled readers because the authors stated: ***"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.
- participants in two of the four groups were informed that "recovery" was possible with those interventions: CBT and GET were promoted 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: participants in the CBT group were informed on five separate occasions in their own CBT Manual that they could ***"overcome their CFS/ME"*** (ie. they could expect to be cured) by the application of CBT. **It should never be suggested to participants in a clinical trial 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.** 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): *"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 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, appears to have been seeking to bias the outcome in favour of the Investigators' favoured interventions which, if successful, would have supported their belief in a psycho-social model of ME/CFS.

- any medical advice given to participants had to be *"compatible with any therapy that the participant is receiving (APT, CBT, GET or SSMC alone)".* Thus the doctor delivering Standardised Specialist Medical Care (which amounted to little more than a "Fatigue Service" clinic doctor -- often a trainee psychiatrist from King's College Hospital -- handing out a leaflet and giving general advice about balancing activity and rest and offering antidepressants) had to give medical advice based not on their clinical assessment or a participant's medical need but in accordance with whatever "therapy" the participant was receiving: ie. if the participant was receiving GET and experienced an exacerbation of symptoms, the doctor had to reassure the participant that this was a normal consequence of using deconditioned muscles. If, however, the participant was in the APT arm of the trial and experienced the same symptoms, the doctor had to tell the participant that they were doing too much and should rest more; **thus participants in the same clinical trial with identical symptoms were to be given differing advice by a clinician that was solely dependent on the particular arm of the trial to which they had been allocated**. The Minutes of the Joint meeting of Trial Steering Committee and Data Monitoring and Ethics Committee held on 27th September 2004 record: "*clinic doctors would be working within a remit of advice and medication they could give"*, a situation that many people deemed unethical.

It cannot be reiterated enough that many people – including not just patients with ME/CFS and their families, but international academics, medical scientists and clinicians who have kept abreast of the biomedical developments in ME/CFS – are deeply dismayed by the apparent abuse of the scientific process that appears to have been condoned and perpetrated by the Medical Research Council, the Principal Investigators and indeed by all those involved with the PACE trial. It is irrefutable that the Wessely School's beliefs about ME/CFS appear not to have advanced with the progression of medical science over the last 25 years.

<u>The chosen entry criteria</u>

The Investigators used entry criteria for the PACE trial that did not define the population they purported to be studying: they used their own "Oxford" criteria, in which the Chief Principal Investigator had a financial interest, as he co-funded them himself. The Oxford criteria have neither the appropriate degree of sensitivity to identify those with ME, nor the specificity to separate them from the wider

"fatigued" population; moreover, the Oxford criteria specifically exclude those with a neurological disorder (and ME is classified as a neurological disorder by the WHO) but the Investigators: *"chose these broad criteria in order to enhance generalisability and recruitment"* (Trial Identifier section 3.6).

On 12th May 2004 a Minister of State, Dr Stephen Ladyman MP, confirmed to an All Party Parliamentary Group that GPs were being offered financial inducements to send people who did not suffer from ME/CFS into the PACE trial.

The use of a heterogeneous population by deliberately including patients who do not have the disorder in question contravenes elementary rules of scientific procedure.

Failure to subgroup the cohort

The Investigators maintained that there would be a secondary analysis using the "London criteria". It is a straightforward fact that if those with a classified neurological disorder were excluded from the outset by strict adherence to the Oxford entry criteria, no amount of "secondary analysis" would reveal those with a classified neurological disorder.

Whilst initially confirming their intention to use the "London criteria" for ME as set out by the late Dr Melvin Ramsay (which required neurological disturbance to be present), sometime between March 2003 and October 2004 the Investigators decided to abandon this and to adopt their own version of the "London criteria".

In contrast to the original Ramsay definition, the Investigators' own version does not require the presence of any neurological disturbance, and this lessened the distinction between true ME and "medically unexplained fatigue" (a somatisation disorder), which accorded with the Investigators' known beliefs and was thus to their advantage.

Even more disturbing is the fact that in the Investigators' own version of the "London criteria", there was no requirement for the pathognomonic symptom of ME (post-exertional exhaustion and malaise) to be present.

All that was left were essentially the Oxford criteria (but with the absence of depression or anxiety), which was an entirely inadequate description of the neurological disease ME.

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 in ME/CFS 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 JPsychiat 1990:156:534-540).

Not a Randomised Controlled Trial as claimed

Although the trial documentation refers to it as an RCT (randomised controlled trial), it was not a controlled trial.

Biases

Known biases may not have been avoided; for example, the assessors knew to which of the intervention groups the participants had been allocated in the trial, such masking being deemed *"impractical"* by the Investigators.

The PACE Trial Manuals

The Manuals used in the PACE trial show that the authors either ignored or did not understand medical science; they were ill-written, often grammatically incorrect, heavily biased towards the Investigators' own beliefs about the nature of ME/CFS (in that no mention was made of the published biomedical underpinnings), lacking in intellectual rigour and were internally inconsistent.

They contained many contradictory claims, for example, they stated that therapists would be treating people *"who generally do too much"* whilst also stating that the PACE trial was based on *"the illness model of both deconditioning and exercise avoidance"* without explaining how people who do too much also suffer from exercise phobia and are deconditioned as a consequence. The manuals recommended going to the pub for a drink as a form of approved recreational activity, whilst also stating that participants' symptoms are exacerbated by alcohol. A "*medical specialist"* in one sentence became a "*therapist"* in the next sentence.

More importantly, the manuals included advice that cannot be considered ethical by any independent and reasonable observer: participants were told to ignore symptoms because they do not result from physical disease: indeed one of the manuals taught therapists how to manage participants who believed they had a physical disease and how to persuade them that this was not the case and to dissuade them from seeking further medical attention. It hardly needs reiterating that patients die from ME.

Therapists were trained not to be honest with participants in that they were to assure participants that they believed ME/CFS to be a "real" (ie. "organic") disease when in fact therapists were taught that it was not an organic disorder but a behavioural disorder.

Speculation was portrayed as fact and assumptions were portrayed as evidence.

A "*warm*" and "*empathetic therapeutic relationship*" between therapist and participant was to be created even though it was not authentic, so participants were deliberately deceived. This contrived "*empathetic"* alliance was designed to undermine the self-confidence of participants, who were instructed by the therapist (who by displaying "*empathy*" thus gained the trust of participants) not to listen to their own bodies; participants were to be repeatedly told that they had thinking errors and that their "*negative thought patterns*" must be challenged; they were to be persuaded that they were not physically ill; that their life-style caused their illness and that the way they managed their illness had prevented them from recovering.

There is no evidence to show that the many pathophysiological abnormalities that have been demonstrated in ME/CFS are caused by wrong illness beliefs or behaviour; on the contrary, there is a significant peer-reviewed evidence-base demonstrating that ME/CFS is a serious, organic, chronic, multi-system disorder.

Failure to adhere to the published protocol

The Investigators failed to adhere to their published protocol and changed it on numerous occasions once the
trial was under way.

This means that they did not report their results according to their original protocol, which is very bad science indeed, as it means their conclusions are not reliable.

Professor White claims that it is common practice to amend a protocol as a trial goes along, but that is not true.

Dr Ben Goldacre of "Bad Science" says of such practice: *"in a trial… you have to say which is the 'primary outcome' before you start: you can't change your mind about what you're counting as your main outcome…. It's not just dodgy, it also messes with the statistics ….You cannot change the rules after the game has started. You cannot even be seen to do that"* (The data belong to the people who gave it to you: The Guardian: 5th January 2008). The fact is that the PACE Investigators did change the rules after the game had started and they have been seen to do that.

Change of entry score once the trial was underway

Eleven months after the trial began, the Investigators changed the entry score on the short form-36 physical function subscale (SF-36 PF) rating from 60 to 65. This was said to be to improve recruitment, which was a problem, but it meant that the trial

included people with better physical functioning scores at baseline than those recruited at the outset.

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 after a trial has started.

This particular change was of key significance in that scores recorded on this same scale played a vital role in assessing outcomes, as people who had higher scores on this scale at baseline required less change during the course of the trial to attain a relatively higher 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.

Objective measures of outcome were dropped

The key objective measure of outcome was dropped: the Investigators 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 Investigators abandoned actigraphy entirely and relied largely on participants' subjective responses to questionnaires, which are notoriously unreliable.

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 significant point is that the Investigators 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 based the outcome of a £5 million study on such patients' personal assessment of their disability (ie. PACE Trial participants were deemed capable of accurately reporting their symptoms/disability).

In other words, the Investigators were satisfied that the only requirement to prove that CBT and GET are effective was for participants (whose judgment the Investigators regard as suspect) to say that they are effective.

Changes in scoring methods

Changes in scoring of participants' self-reported measures of fatigue were also not reported as per the protocol: when post-intervention changes are so small, they do not register on the scale originally chosen by the Investigators, so the Investigators

introduced a different scoring method which enabled them to show a small statistical (but not clinical) improvement.

The six minute walking test (6MWT)

A secondary outcome measure was the 6 minute walking distance test (6MWT). In their protocol, the Investigators stated: "*The six-minute walking test will give an objective measure of physical capacity"* and they cited the American Thoracic Society's 2002 guidelines: "*The walking course must be 30 metres in length".*

The ability of such a test to assess capacity in ME/CFS is highly debatable, as it fails to take into account the cardinal feature of ME/CFS (post-exertional fatigability and malaise).

The Chief Principal Investigator himself has published evidence supporting the need for serial post-exercise testing in ME/CFS (JCFS 2004:12:(2):51-66) but that did not happen in the PACE trial; even though one of the cited references (BMJ 1982:284:1607-1608) stipulates that the 6MWT needs to be carried out twice to achieve reproducible results, the Investigators did not do so and provided no credible reason for not incorporating repeat testing in the trial design.

Further, the 6MWT is known to have low test-retest reliability (even more so in this case, as the assessors were not blinded and knew to which of the intervention groups participants had been allocated).

The results of the 6MWT were dismal: the mean (ie. average) distance recorded by those who had undergone CBT was 354 metres and for those who had undergone GET the mean distance was 379 metres, the latter being only a 67-metre increase from baseline after one year's therapy.

These scores were 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) and the mean score of those in class III heart failure is 402 metres.

PACE trial participants (whose average age was 38) did not achieve a mean six minute walking distance of 518 metres, a level considered abnormal for healthy people aged 50-85 years.

If PACE participants could not achieve a one-off result achievable by healthy people of 85, then there is little hope that they can function adequately in real life and the Investigators' proclamations of "recovery" are insupportable.

Moreover, data on the 6MWT were available for only 69% - 76% of participants, a completion figure roughly 20% lower than for the other secondary outcome measures, for which the Investigators offer no explanation.

Significantly, the CBT group managed less of an average increase in walking distance than those in the SMC alone group.

The Chief Principal Investigator has attempted to justify such poor results by blaming the short length of the corridor used to carry out the test, which was only 10 metres (not the required 30 metres): conceding that there was a need for a greater number of turns than was usual, he said that, because of concern for participants, they were not given encouragement to walk faster.

It is possible that the Chief Investigator chose not to repeat the 6MWT in light of the UK Chief Medical Officer's Working Group Report of 2002 (from whose expert group he and Trudie Chalder walked out when it became clear that they were not going to achieve their aim of definitively categorising ME/CFS as a behavioural disorder); that report was clear: ***"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…has a characteristically delayed impact"***. This being so, the results of a re-test were likely to have been even worse.

The results of the 6MWT are significant and cannot be explained away as the Investigators have attempted to do by claiming that: *"recovery from chronic fatigue syndrome (CFS), which is defined by a patient's reported symptoms, is arguably best measured by multiple patient-reported outcome measures, rather than a single performance test"* (http://www.meassociation.org.uk/2013/07/pace-trial-letters-and-reply-journal-of-psychological-medicine-august-2013/).

Such views are at variance with other international researchers' findings in ME/CFS, who have demonstrated that patients' subjective reports do not correlate well with objective measures of activity.

Such views are also at variance with the Investigators' own published views: "*Objective measures of physical activity have been found previously to correlate poorly with self-reported outcomes"* (Psychological Medicine 2013: Oct; 43(10):2227-35; Epub ahead of print).

The 6MWT was the only allegedly "objective" outcome measure and it showed that the PACE trial interventions CBT and GET were not effective in the cohort studied.

Furthermore, the PACE Trial walking test gave no indication for how long participants could maintain the walking speed beyond the 6 minute test, nor if they suffered from post-exertional exhaustion, nor any indication of participants' walking ability over a longer time frame, or if they experienced exacerbation of other symptoms.

<u>Changes to the "positive outcome" score</u>

Initially the Investigators decided in 2002 that an SF-36 physical function (SF-36 PF) score of 75 would indicate a "positive outcome" (which is not the same as "recovery"); in 2006 this was lowered to 70 but after the trial had finished, the Investigators dropped their "positive outcome" analysis altogether.

The Investigators' chosen "normal range" for their *post-hoc* analysis

The Investigators' deviation from the protocol in terms of entry scores meant that ratings which would qualify a person as being sufficiently impaired to enter the trial overlapped with those considered "within the normal range" when assessed on completion of the trial.

The illogical situation whereby participants could score worse on completion than on entry but still be classed as being within the "normal range" as a result of the alleged efficacy of the interventions arose because of the Investigators' *post-hoc* changes, revisions and re-calculations and their failure to use the benchmarks to which they had committed themselves in the protocol.

Changes were made by the Investigators in their reference material on which they relied for a comparative group for their "normal range"; in fact they used a highly questionable comparison group to obtain their "normal range" for use in the PACE trial.

In his application dated 12th September 2002 to the West Midlands Multicentre Ethics Committee (MREC) seeking permission to amend the approved protocol, Professor White described the derivation of his new threshold of "normal" as follows: *"We will count a score of 75 [out of a maximum of 100] or more as indicating normal function, this score being one standard deviation below the mean score [90] for the UK working age population"*, citing Jenkinson C et al (BMJ:1993:306:1437-1440) and this paper was cited in the trial protocol references.

However, in their Lancet article the Investigators made no mention of that paper; instead they relied on Bowling et al (J Publ Health Med 1999:21:255-270) as the source of their "normal range", citing a mean (ie. average) for the UK working age population of an SF-36 PF score of 84 with an SD (standard deviation) of 24, making 60 the threshold of their chosen "normal range" for the PACE trial (although Bowling et al do not use the term "normal range").

The "normal range" is not the same as "normal" function as generally understood; the former is a statistical concept whereas in lay terms the latter implies high physical function with no impairment.

In statistical terms, the "normal range" is the mean plus/minus one standard deviation from the mean; when data is equally distributed round a mean, the

concept relates well to what is the norm. However, health in the general population is not normally distributed around a mean but skewed towards the top end of the scale – a fact to which Bowling et al drew specific attention. In other words, good health is the norm and it is not possible to be above the range of normal on the SF-36 physical function subscale.

The Investigators' chosen threshold for their "normal range" fails to deliver a meaningful indication of PACE participants' physical function; it was unduly low in relation to physical function and requires scrutiny.

In their Lancet article the Investigators describe their comparison group as being the working age population but the data set analysed by Bowling et al on which the investigators rely relates to the adult population as a whole, not the working age population, and the adult population includes elderly adults (in fact it included everyone aged between 16 and 85+), thus lowering the threshold of the "normal range" and thereby boosting the proportion of PACE participants who could be deemed to have improved on conclusion of the trial.

When this was pointed out to him, the Chief Principal Investigator had no option but to acknowledge that: "*We did, however, make a descriptive error in referring to the sample we referred to in the paper as a 'UK working age population', whereas it should have read 'English adult population'".* Even so, this was an inappropriate comparator to have used in relation to PACE trial participants (whose average age, as noted, was 38).

Any source that relates to the general population as a whole will include those who are beyond working age, the very old, and the chronically or short-term sick. The appropriate comparison group for PACE participants should have been the SF-36 physical function scores for age and sex-matched healthy adults of working age.

If the threshold of the Investigators' "normal range" were to have been set any higher, it would have been more difficult – if not impossible – for them to claim even moderate success for the PACE trial.

Turning to the other primary outcome measure (the fatigue score), a participant could have entered the PACE trial with a bimodal fatigue score of 6 and left the trial with a score of 7, 8 or 9 (ie. with greater fatigue) yet still fall within the Investigators' own *post-hoc* "normal range".

Because on 17th February 2011 some PACE participants' achievement of the Investigators chosen "normal range" was presented to the media (and hence to the public) as equating to "normal" by one of the Investigators (Professor Trudie Chalder) at the Science Media Centre press briefing on the PACE trial results, this was interpreted as "recovery". This was not surprising, as her words were: "*Twice as many people on graded exercise therapy and cognitive behaviour therapy got back to normal".*

This was widely reported by the media the following day; for example, The Guardian's health correspondent proclaimed: *"More people recover if they are helped to try to do more than they think they can"* (18th February 2011). Other newspapers and outlets followed suit: *"Got ME? Just get out and exercise, say scientists"* (The Independent); *"Got ME? Fatigued patients who go out and exercise have best hope of recovery, finds study. Scientists have found encouraging people with ME to push themselves to their limits gives the best hope of recovery"* (Daily Mail); *"Exercise and therapy can reverse effects of ME"* (The Daily Record); online medical sources such as NHS Choices and NHS Evidence also exaggerated the reports of a successful outcome, as did The Lancet.

Because of numerous complaints about the misrepresentation of "recovery" in the media and the medical press, the Investigators were obliged to write to The Lancet confirming that: "*Being within a 'normal range' is not necessarily the same as being recovered"*, but the harm had been done.

In the same issue as the Investigators' article, The Lancet carried a Comment by two Dutch clinical psychologists, Professors Gijs Bleijenberg and Hans Knoop, with both of whom Professor White had previously co-authored published papers on "CFS"; indeed, Gijs Bleijenberg was one of the authors of a manual on which the PACE trial's own CBT manual was based. Bleijenberg and Knoop claimed – erroneously – that: "*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 was blatantly wrong, because not only did the Investigators not use a *"healthy person's score"* as a comparator, but no recovery figures had been published.

It has been confirmed by The Lancet that Professor Peter White himself had been shown the Dutch authors' Comment before publication and had approved it for publication; it was unquestionably wrong, so it is unclear why he approved it unless he badly wanted the message of "30% recovery" to hit the medical headlines as well as the media.

The Lancet was subsequently admonished by the Press Complaints Commission (PCC) for failing to take care not to publish inaccurate or misleading information and for breaching Clause 1 (Accuracy) of the Editors' Code of Practice. The PCC adjudication said that Bleijenberg and Knoop had "*failed to make clear that the 30 per cent figure for "recovery" reflected their view that function within "normal range" was an appropriate way of "operationalising" recovery – rather than statistical analysis by the researchers based on the definition for recovery provided. This was a distinction of significance, particularly in the context of a comment on a clinical trial published in a medical journal".*

Having shamefully misrepresented the successful outcome of the PACE trial at its press briefing, the Science Media Centre – which claims to promote accurate coverage of science -- did not ensure that this was reported in the media;

furthermore, the reason that the Countess of Mar had to resort to the Press Complaints Commission was that The Lancet, having at first acknowledged in writing that it would have to correct the error in the Comment, repeatedly refused to do so after consultation with Professor White.

<u>"Recovery" scores</u>

As noted, the "normal range" does not equate with "normal" health and it certainly does not equate with "recovery" from ME/CFS.

In the Investigators' original definition of "recovery" as set out in their protocol, a participant had to achieve a score of 85 or above on the SF-36 physical function subscale; however, when selective results of the trial were published in The Lancet and Psychological Medicine, the Investigators chose to abandon the statistical analysis set out in the trial's protocol and instead constructed a set of *post-hoc* metrics by which the success of the interventions were to be assessed.

The *post-hoc* metric for physical function warrants close scrutiny because its derivation contains a significant statistical error and its description in both journals in misleading.

In Psychological Medicine White et al wrote: *"We changed our original protocol's threshold score for being within a normal range on this measure from a score of >=85 to a lower score as that threshold would mean that approximately half the general working age population would fall outside the normal range. The mean (SD) scores for a demographically representative English adult population were 86.3 (22.5) for males and 81.8 (25.7) for females (Bowling et al 1999). We derived a mean (SD) score of 84 (24) for the whole sample, giving a normal range of 60 or above for physical function*" (Psychological Medicine 2013: Oct; 43(10):2227-35: Epub ahead of print).

This statement proved to be inaccurate.

It is clear that from the start of the trial Professor White et al had two distinct concepts in mind: "positive outcome" (defined as the mean SF-36 PF score minus 1 SD or above) and "recovery" (a higher threshold defined as an SF-36 PF score of 85 or above).

It is instructive to note the progressive widening of these thresholds over time:

Year	Source	Mean minus 1 SD	Positive Outcome	Recovery
2002	Trial protocol	75 [1]	75	not specified
2007	Trial protocol	70 [2]	75	>=85
2011	Lancet	60	60	not specified
2013	Psych Med	60	>=60	>=60

[1] 2002: *"We will count a score of 75 [out of a maximum of 100] or more as indicating normal function, this score being one standard deviation below the mean score [90] for the UK working age population"*

[2] 2007: *"A score of 70 is about one standard deviation below the mean score (about 85, depending on the study) for the UK adult population".*

Therefore it can be seen that between 2002 and 2011-2013 the Investigators' derivation of the mean SF-36 PF score minus 1SD fell from a score of 75 or above to a score of 60 or above. Similarly, their definition of recovery fell from a score of 85 or above to a score of only 60 or above.

Consequently, by publication, there was no difference between a positive outcome and recovery, both of which fell under the common rubric of the Investigators' chosen "normal range".

Not only do the published results lack conceptual clarity, they also contain an important statistical error. The Investigators' stated justification for reducing the SF-36 physical function threshold of the "normal range" from 85 to 60 (namely that approximately half the general working age population would fall below an SF-36 physical function threshold of 85) is not supported by any cited reference and specifically not by Bowling et al, although it appears possible that the Investigators intended readers to assume that they were relying Bowling et al for that statement.

Independent re-analysis of Bowling's raw data shows that just 18% (not approximately 50% as claimed by the PACE Investigators) fall below an SF-36 physical function threshold of 85, and once those with long-term health issues are excluded, the figure falls to 8%. These figures are nowhere near the figure of approximately 50% upon which the Investigators relied. In fact, at least half the UK working age population have an SF-36 physical function score of 100 according to Bowling et al.

This vitiates the Investigators' stated reason for lowering the score from 85 to 60 and consequently invalidates the conclusion of their published paper on "recovery" (Psychological Medicine 2013: Oct; 43(10):2227-35: Epub ahead of print).

The Investigators did not use normalised scoring of the SF-36 physical function subscale; instead, they asked ten questions, each scoring a maximum of ten points, so the maximum score for someone reporting no physical disability was 100. The Investigators claim that, when scored in this way, and apparently relying on Bowling et al, a PACE participant could be described as recovered if they had a score of 60 or above out of 100.

The new threshold of 60 is noteworthy because it is lower than the score of 65 required for entry to the trial, so a participant could deteriorate or stay the same but still be counted as recovered in the published results.

This has resulted in an explicit contradiction by the Investigators because, having set the lower bound for recovery at 60, they also state in the same paper that any SF-36 score of less than or equal to 65 represents abnormal physical function, therefore, in the same paper, scores of 60 and 65 represent both abnormal physical function and recovery.

This is not just a theoretical concern, as an FOIA request revealed that nearly 13% of participants had scores of 60 or 65 when they entered the trial: if 13% entered the trial with "normal" function, why were they treated?

When the Investigators' paper on "recovery" was published in January 2013 in Psychological Medicine, the internet was awash with incredulity, for example:

- "*I wonder how this got through peer review"*

- "*If you look at the distribution plot in Bowling they are not Gaussian* (a Gaussian graph is typically bell- shaped) *and hence SD* (standard deviation) *is meaningless anyway, so (they) shouldn't be allowed to use it to generate (their) threshold. How can a senior statistician from the MRC get things so very wrong?"*

- "*The degree of scientific and mathematical illiteracy…is appalling. The most basic stuff we teach in General Science to teenagers seems to be lacking…don't draw conclusions beyond your data, and most basic of all, opinions are not fact. I don't even want to go into their abuse, misuse and general ignorance about statistical analysis of data"*

- *"White et al stated in their recent response…that changes to the trial protocol were approved independently by two trial oversight committees….It would be rather concerning if such a basic error managed to pass three groups of professionals involved with the PACE trial, not to mention being unspotted by multiple peer-reviewers in at least two journals, including The Lancet, after what its editor in chief described as 'endless rounds of peer review' "*.

It is important to be aware that the figure of 60 for "recovery" was used by the Investigators specifically for the PACE trial and it contradicts how they themselves previously defined markers of recovery in the same disorder using the same measure: in 2007 they stated: *"A patient had to score 80 or higher to be considered as recovered"* (Psychother Psychosom 2007:76:171-176) and in 2009 their Dutch colleagues asserted: "*A cut-off of less than or equal to 65 was considered to reflect severe problems with physical functioning"* (European Journal of Public Health 2009:20:3:251-257).

Common sense would suggest that a mathematically-derived recovery threshold which allows a participant to deteriorate and still be described as recovered must contain a mistake. Yet common sense has not prevailed in this instance and the co-

editor-in-chief of Psychological Medicine (Professor Sir Robin Murray, Professor of Psychiatric Research at The Institute of Psychiatry; Fellow of the Royal College of Psychiatrists; elected a Fellow of the Royal Society in 2010 and knighted in 2011 for his services to medicine), has declined to correct obvious errors when they were pointed out to him.

No reduction in State or insurance benefits claimed

The Investigators and the DWP anticipated that there would be a reduction in participants' benefit uptake at the conclusion of the PACE trial on the basis that participants claiming such benefits would be able to return to gainful employment, whereas in fact there was an increase in benefit uptake from baseline to follow-up (Adaptive Pacing, Cognitive Behaviour Therapy, Graded Exercise, and Specialist Medical Care for Chronic Fatigue Syndrome: A Cost-Effectiveness Analysis. McCrone P et al. PLoS ONE Aug 2012:7(8):e40808), hence the DWP got no return on its investment in the PACE trial.

Client Service Receipt Inventory and the Investigators' refusal to release data owned by tax payers (who funded the PACE trial)

A basic tenet of scientific research is that data generated in a clinical trial is made available to other scientists for the ultimate benefit of sick people.

Currently there is a campaign being run by Dr Ben Goldacre of "Bad Science" and the major UK medical journals calling for all data from all clinical trials to be made public, with participating journals saying they will not publish the results unless all data, suitably anonymised, are made available.

Even though they do not own the data – since the PACE trial was funded by UK taxpayers -- the Investigators have persistently refused to comply with this requirement, which is why interested parties have made numerous FOIA requests.

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*".

The Investigators collected the data but have not delivered what was required in that they have not published the number of participants who were able to return to gainful employment or education at the conclusion of the PACE trial. Despite numerous requests for the number of participants who were able to return to (or be available for) full-time employment, the Investigators repeatedly refuse to supply these important figures.

The figures may never be obtained, since in a FOIA request for withheld PACE trial data, the Judge in the UK Information Rights Tribunal Appeal Judgment on Appeal

No: EA/2013/0019 handed down on 22nd August 2013 ruled that *"academic freedom"* takes precedence over individual (or public) interest.

The Investigators justified their failure to provide the return to employment figures thus: "*Return to work is not, however, an appropriate measure of recovery if the participant was not working before their illness"* (Recovery from chronic fatigue syndrome after treatments given in the PACE trial. PD White et al. Psychological Medicine 2013: Oct; 43(10):2227-35 Epub ahead of print).

This raises the issue of why the Investigators included it as a measurement of successful outcome in their original protocol.

When it was pointed out by the Medical Advisor to the ME Association in a letter to Psychological Medicine that such figures would have constituted a useful measurement of recovery, Professor Peter White attempted to defend this failure: "*follow-up at six months after the end of therapy may be too short a period to affect either benefits or employment. We therefore disagree with Shepherd that such outcomes constitute a useful component of recovery in the PACE trial"* (http://www.meassociation.org.uk/2013/07/pace-trial-letters-and-reply-journal-of-psychological-medicine-august-2013/).

The Clinical Global Impression (CGI)

Out of the reports submitted on the participant-rated CGI (clinical global impression) of change in overall health at the end of the trial, 60% of participants in the GET group and 58% of participants in the CBT group reported negative or minimal change.

The Investigators were not, after all, studying ME/CFS

The PACE trial Patient Clinic Leaflet that encouraged patients to become participants stated: "*Chronic fatigue syndrome"* is *"also known as post-viral fatigue syndrome, myalgic encephalomyelitis (ME) or myalgic encephalopathy (ME)"*, thus there can be no doubt that patients with the neuroimmune disease ME were alleged to have been included in the PACE trial.

Not only did the Investigators remove the requirement for the pathognomonic feature of ME from their own (diluted) version of the "London criteria" (so that it was effectively the same as their own Oxford criteria), but because of significant problems with recruitment, on 14th July 2006 Professor Peter White sought approval from the West Midlands Multicentre Ethics Committee to advertise his PACE trial to doctors, asking them to refer anyone *"whose main complaint is fatigue (or a synonym)"* to enter the trial.

ME/CFS is a classified nosological entity in the WHO International Classification of

Diseases in which the pathognomonic feature is post-exertional fatigability; this is very different from "fatigue", so just how scientifically rigorous the inclusion of patients with "*fatigue (or a synonym)"* in a clinical trial that claimed to be studying ME/CFS might be has not been addressed by the Investigators.

The Investigators focused only on "fatigue" and ignored other significant and well-documented signs and symptoms associated with cardiovascular, respiratory, neurological, endocrinological, immunological, gastro-intestinal and musculo-skeletal system dysfunction; in particular, the Investigators disregarded the robust literature on vascular and inflammatory problems in ME and the documented increased risk of cardiovascular events in relation to exercise in patients with ME.

Ethical approval and funding were granted on the basis that the Investigators would be studying "CFS/ME", but after the trial ended and selected results had been published in The Lancet, in March 2011 Professor Peter White wrote to the editor of The Lancet saying: "*The PACE trial paper…does not purport to be studying CFS/ME but CFS defined simply as a principal complaint of fatigue".*

A "*principal complaint of fatigue*" is not ME/CFS (a classified neurological disorder in ICD-10 at G93.3), yet the Investigators stated in The Lancet: *"The PACE findings can be generalised to patients who also meet alternative diagnostic criteria for chronic fatigue syndrome and myalgic encephalomyelitis"* (The Lancet: February 18, 2011: DOI:10.1016/SO140-6736(11)60096-2).

To regard and manage them – whatever definition used -- as a single behavioural disorder is a cause for concern because interventions that may be suitable for those with chronic "fatigue" may be harmful and even fatal for someone with ME/CFS.

<u>Professor White's belief about ME/CFS</u>

Professor White's belief about ME/CFS is contained in his contribution to the standard medical textbook (Clinical Medicine, edited by Kumar and Clark) in which ME/CFS is listed under "Functional or Psychsomatic Disorders: Medically Unexplained Symptoms", which Professor White states were previously known as " '*all in the mind'; imaginary and malingering".*

In June 2004 Professor White was awarded an OBE for his work on "CFS". The citation was: "*For services to medical education"*. Notices circulating at the time proclaimed him as leading the research into CFS/ME and said his OBE was a *"well-deserved honour and acknowledgement of his contribution to work on CFS/ME".*

For someone to receive such an honour seems surprising if the person so honoured is apparently ignorant of the established facts pertaining to the subject of his research interest for which he was honoured.

Almost a decade later, despite the emerging biomedical science that further disproves his beliefs about the non-organic basis of ME/CFS, his beliefs remain entrenched and have not changed with the advancement of medical science.

The peer-reviewed research data do not support his beliefs that ME/CFS is a functional somatic syndrome; on the contrary they disprove his beliefs because there is clear and convincing evidence of organic abnormalities in ME/CFS, including evidence of:

disrupted biology at cell membrane level; **abnormal brain metabolism**; widespread cerebral hypoperfusion; **central nervous system inflammation and demyelination;** hypomyelination; **a complex, serious multi-system autoimmune disorder**; significant neutrophil apoptosis; **a chronically activated immune syste**m (eg. the CD4:CD8 ratio may be grossly elevated); diminished NK cell activity; **abnormal vascular biology, with disrupted endothelial function; significantly elevated levels of isoprostanes; cardiac insufficiency -- patients are in a form of cardiac failure;** autonomic dysfunction (thermodysregulation; frequency of micturition with nocturia; labile blood pressure; pooling of blood in the lower limbs; reduced blood volume with orthostatic tachycardia and orthostatic hypotension); **respiratory dysfunction, with reduced lung function in all parameters tested**; neuroendocrine dysfunction (notably HPA axis dysfunction); **recovery rates for oxygen saturation that are 60% lower than those in normal controls; delayed recovery of muscles after exercise** (note: there is no evidence of deconditioning); **evidence of a sensitive marker of muscle inflammation;** reduced size of the adrenal glands by 50%, with **reduced cortisol levels**; evidence that up to 92% of ME/CFS patients also have irritable bowel syndrome (IBS); **at least 35 abnormal genes (acquired, not hereditary), specifically those that are important in energy metabolism; there are more abnormal genes in ME/CFS than there are in cancer; serious cognitive impairment (worse than occurs in AIDS dementia); adverse reactions to medicinal drugs, especially those acting on the CNS**; symptoms fluctuating from day to day and even from hour to hour. There is no evidence that ME/CFS is a psychiatric or behavioural disorder.

For individual references, see: (i) www.meactionuk.org.uk/Organic_evidence_for_Gibson.htm and (ii) www.meactionuk.org.uk/What_the_Experts_say_about_ME.htm).

Many people around the world (ie. not just in the UK) believe that there is a pressing need for the removal of those currently in charge of the ME/CFS programme in the UK because, as Professor Stephen Holgate, MRC Clinical Professor of Immunopharmacology and Honorary Consultant Physician at the University of Southampton
said at the CFS/ME Workshop held on 19th/20th November 2009 at Heythrop Park, Banbury, near Oxford: **it is time to get away from old models and to use proper science**.

On 2nd July 2013 Professor Holgate addressed the Forward ME Group in the House of Lords; **he called for radical change in ME/CFS research and said some researchers new to the field had been shocked by the poor quality of much ME/CFS research; he commented that some individuals had "*made a career*" out of ME/CFS theories that could be shaky and it was clear that this had to change** (http://www.meassociation.org.uk/?p=16383).

Such change has not yet happened and Professor White's influence remains intact: in the UK Information Rights Tribunal Appeal Judgment on Appeal No: EA/2013/0019 handed down on 22nd August 2013 in which the Appellant sought information on the PACE trial under the FOIA, the Judge stated that Professor White *"listed the considerable commitment he had to make on a continual basis to defend and justify his work"* and quoted Professor White's evidence: *" 'I have had to provide responses to Parliamentary Questions from members of both Houses of Parliament to allow them to understand the nature and findings of the PACE trial. In particular, I had to recently brief several members of the House of Lords so that they might speak in a critical debate about the PACE trial held on 6th February this year' ".*

This explains why the House of Lords "debate" on 6th February 2013 was not a debate at all on the issues raised by the Countess of Mar but merely a platform for undiluted praise of the PACE trial and why the Medical Advisor to the ME Association had cause to write on 8th February 2013 on an internet forum: "*I was at the House of Lords …for the debate. Sadly, I thought it was a very disappointing debate because after the Countess of Mar had made her speech, everyone else basically just read out prepared speeches with gave uncritical support to all aspects of the PACE trial".*

What remains unaddressed by Professor White and his colleagues who favour the "behavioural model" of ME/CFS is <u>why</u> there have been so many questions raising concerns about his work on ME/CFS in both Houses of Parliament and <u>why</u> he has had to "*defend and justify his work"* on *"a continual basis".*

Given that for nine months between February and October 2010 Professor White was granted leave of absence while he completed the PACE trial (necessitating the employment of locum Consultant cover for him at Barts), such leave of absence may have afforded Professor White enough time to address the legitimate issues raised with the transparency and speed required by his funding bodies.

In its Terms and Conditions relating to its grants, MRC-funded authors have a responsibility to report accurately and without obfuscation, and the MRC requires grant-holders to adhere to its policy on data-sharing which is built on the OECD report "Promoting Access to Public Research Data for Scientific, Economic and Social Development". That report identified that publicly-funded research data are "*a public good, produced in the public interest and should be openly available to the maximum extent possible*". The MRC specifically states that it expects *"valuable data arising from MRC-funded research to be made available to the scientific community with as few restrictions as possible so as to maximise the value of the data for research and for eventual patient and public benefit"* and that such data

"must be shared in a timely and responsible manner". It also states: "*Our data-sharing policy applies to all MRC-funded research"*; and it requires that results from this data-sharing *"should meet the high standards of all MRC research regarding scientific quality, ethical requirements and value for money".*

Clearly, special pleading must relate to the PACE trial, as those Terms and Conditions have not been met by the PACE trial Investigators, yet they have not been subjected to any admonishment for their failure to comply with the MRC's own stipulations.

For the last 25 years, Professors White, Sharpe, Chalder and Wessely have insisted that ME is not an organic disease and their extensive published outcome provides evidence of their beliefs.

Those beliefs are at variance not only with the substantial biomedical evidence-base on ME/CFS that has emerged since the 1980s but also with the evidence of the world's premier virologist, Dr Ian Lipkin, Professor of Neurology and Pathology and Director of the Centre for Infection and Immunity at Columbia University, who has recently publicised his current work on ME/CFS: *"Many of these patients had evidence of immunity inflammation….the primary cause which I still believe is likely to be an infectious agent"*.

Professor Lipkin referred to the dismissal of ME/CFS as a psychological illness and to his own work on ME/CFS in 1997: *"As many of you will recall, there was a very strong sentiment in some portions of the scientific community, not all of it, that this is a psychological illness….Based on our findings, we had very strong evidence that people with Chronic Fatigue Syndrome are ill. It was a real, physical illness and they deserved a deep dive to find out why they were ill".*

He concluded: *"Our evidence suggests, based on the cytokines…that there is, in fact, ongoing stimulus to the immune system which results in activation and may well account for many of the symptoms associated with the disease"* (CDC PCOCA Conference Call, 9th September 2013).

Two years previously, reporting in November 2011 on their work on ME/CFS using multiple deep sequencing platforms, Professors Ian Lipkin and Mady Hornig were clear: Professor Hornig said they had good reason to believe there was an infectious trigger and both Professors Lipkin and Hornig stated that they do not consider ME/CFS to be psychosomatic: Professor Hornig said: "*It's very difficult in my mind to make this a psychological disorder....that shouldn't ever be viewed as being the primary problem"* (Cure Talk; ME Association website, 4th November 2011).

It is worth reiterating that it was thirteen years ago that Professor Anthony Komaroff, Professor of Medicine at Harvard, said: "***There is now considerable evidence of an underlying biological process which is inconsistent with the hypothesis that (ME/CFS) involves symptoms that are only imagined or amplified because of underlying psychiatric distress. It is time to put that hypothesis to rest***" (Am J Med 2000:108:99-105).

Even fellow psychiatrists now point out: "*a purely cognitive-behavioural model of CFS seems less explanatory for the pathophysiological disturbances identified so far…Nonetheless, the (behavioural) model is the main rationale of cognitive-behavioural therapy (CBT) and graded exercise training (GET) which are currently both recommended as first-line treatments"* (Boudewijn Van Houdenhove et al; Fatigue: Biomedicine, Health & Behaviour: doi:10.1080/21641846.2013.795085).

The PACE Investigators and those who share their beliefs about ME/CFS are clearly wrong in their assertion that ME/CFS is a psychological disorder and the very poor results of the PACE trial serve to substantiate how wrong they are.

<u>In summary:</u>

Despite the enormity of the media/medical spin on "recovery" surrounding it, the duplicitous utterances and excuses, and all the re-calculations of the data, the PACE trial failed.

It was wrong to focus on the small number of participants who, it is alleged, made a moderate improvement (which the Investigators themselves admit may not be maintained over time) whilst totally ignoring the vast majority (roughly two thirds) who were not helped by the interventions.

The PACE trial protocol claimed: "*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…of the most widely advocated treatments for CFS/ME".*

It was one of the PACE Principal Investigators themselves, Professor Michael Sharpe, who went on record about the results of the PACE trial; on 18th April 2011 he said on Australian radio: "*What this trial isn't able to answer is how much better are these treatments than really not having very much treatment at all".*

<u>The Science Media Centre's misrepresentation of the PACE trial results to the media</u>

The emanations from the Science Media Centre (SMC) may be accepted by informed observers to be suspect because it represents only one narrow section of the scientific community (http://ngin.tripod.com/020602c.htm) but its wildly exaggerated press briefing for the PACE trial on 17th February 2011 was a travesty *par excellence.*

The SMC produced 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 – who were involved in the PACE trial itself. 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 22nd 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 7th July 2006).

- Dr (now Professor) 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.

(On 25th September 2013 NICE confirmed that they will not be reviewing their 2007 Guideline on CFS and that it is to be placed on their "static" list of guidelines that require only occasional revisiting instead up regular up-dating).

The Science Media Centre has been absolutely fundamental in misrepresenting and acclaiming the results of the PACE trial to the media. At the PACE trial press briefing, a number of grossly inflated and quite unjustified claims were made that are not supported by evidence and the Science Media Centre supplied and publicised quotations only from people with known and indisputable biases and with vested interests in maintaining the misperception of ME/CFS as a functional (behavioural) disorder.

The SMC's press briefing did not address how it is acceptable for a trial to be hailed as the "gold standard" when, even after numerous deviations from the protocol and many re-calculations of thresholds, it resulted only in moderate benefit to around 10% - 15% of participants over and above the benefit of standard medical care.

In fact, 70% - 72% of all participants were not in the Investigators' chosen (unduly low) "normal range" for fatigue and physical functioning at the end of the trial. The participants' own views of their improvement were much less positive than the spin given in the SMC press briefing – roughly two thirds said that they had little or no improvement in their overall health but this was not reported in the media.

Consideration of the PACE trial data dispels the assertions quoted above so it was essential for the protection of vulnerable patients that a more balanced interpretation of the PACE trial findings was supplied to the media and thus entered the public domain, but the Science Media Centre did not ensure any such dissemination.

Following publication of selective results of the PACE trial in The Lancet, Swiss Re's UK Life & Health Claims team arranged a web-based training session with Professor Peter White; it was called "Managing claims for fatigue the active way" and it was explicit: "*It will likely take time before the general public and some medical professionals accept the findings of this research….Key takeaways for claims management….**It is likely that input will be required to change a claimant's beliefs***

about his or her condition *and the effectiveness of active rehabilitation",* hence the PACE trial Investigators' deceptions about ME/CFS are not merely an academic matter: they have led to vile sentiments such as these, where it becomes acceptable practice for insurers to coerce sick people into believing things that are demonstrably untrue.

Another key takeaway for claims managers said: *"A final point specific to claims assessors, and a question we're often asked, is whether CFS would fall within a mental health exclusion, if one applies to the policy. The answer to this lies within the precise exclusion wording. If the policy refers to functional somatic syndromes in addition to mental health, then CFS may fall within the exclusion….The point made is that a diagnosis of ME is considered a neurological condition according to the arrangement of the ICD…whereas CFS can alternatively be defined as neurasthenia which is in the mental health chapter of ICD-10".*

These psychiatrists who work for the insurance industry have been notified more than once that their assertion that ME/CFS has dual classification in the WHO International Classification of Diseases (once in the Neurological Section at G93.3 and also in the Mental (Behavioural) Section at F48.0) is incorrect. Their false assertions have been repudiated by the WHO, who on 23rd January 2004 confirmed in writing*: **"According to the taxonomic principles governing ICD-10, it is not permitted for the same condition to be classified to more than one rubric".*** The WHO further confirmed that this means that ME/CFS **cannot** be known as or included with neurasthenia or any other mental or behavioural disorder, as ME/CFS is a distinct nosological disorder.

The readily-provable facts are that the PACE Investigators who work for the insurance industry pay no heed to the WHO classification, to scientific exactitude, to an international biomedical evidence-base on ME/CFS, nor to patients with ME/CFS because, it appears, profits must take precedence over patients.