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From Malcolm Hooper Ph.D.,B.Pharm.,C.Chem.,MRIC

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Chief Scientific Adviser to the Gulf Veterans' Association

President: the National Gulf War Veterans and Families Association, NGVFA, (2002)

Dr Frances Rawle

Head of Corporate Governance and Policy

Medical Research Council

14th Floor

One Kemble Street

London WC2B 4AN

26th January 2011

Dear Dr Rawle

Re: Complaint about MRC PACE Trial

This is to acknowledge your much-delayed letter dated 6th January 2011 which I did not receive until 20th January 2011.

I found your response to be disappointing and unconvincing; not only was it dismissive, it proceeded by assertion and denial whilst not providing any reasoned consideration or evidence to counter the substantial and secure evidence-base set out in my complaint.

Despite your conclusion that none of my complaints can be upheld because you believe they are groundless and without substance -- and you state you will not be taking further action -- the matter is not concluded, as you have failed to address the issues set out in the complaint. The MRC's total rejection of my complaint should not be based on what you believe, but on the facts with which you were provided. Nowhere did I draw attention to scientific facts that can be disputed by evidence rather than by belief.

You start by saying: *"Your letter to Dr Roberts implies that you wish us to focus our response on concerns relating to the PACE Trial"*. My complaint, both the report (Magical Medicine: how to make a disease disappear) and the accompanying letter, clearly set out that the entire complaint was about the PACE Trial. Your inference reveals an extraordinary misunderstanding of the substance of my complaint.

Your response would have been more believable if you had taken seriously even one point of the complaint; the fact that you have dismissed all the concerns indicates that you have not really attempted to take any of them seriously.

Nowhere in your letter is there an acknowledgement of the WHO ICD classification since 1969 of ME/CFS as a neurological disorder, a disorder that was recognised as organic by the Royal Society of Medicine in 1978 and by the Department of Health in 1987, and a disorder which in 2002 the Chief Medical Officer said should be set alongside multiple sclerosis, MS, and motor neurone disease, MND.

Nowhere is there any acknowledgment of the biomedical nature of ME/CFS as a chronic inflammatory multi-system disorder.

It is clear that you are not talking about ME/CFS (the alleged subject of the PACE Trial) at all, yet the results of the PACE Trial will be applied to those with ME/CFS. Which other classified neurological disorder has behavioural modification as the primary -- indeed the only -- intervention?

You state that from your reading of my report, you have reduced my main concerns to three: (1) MRC funding of the PACE Trial; (2) potential harmful effects of the interventions and (3) allegations of misrepresentation and coercion, none of which you have addressed satisfactorily and you have ignored many other important and justified concerns entirely.

May I remind you briefly of the listed concerns, which were clearly enumerated in "Conclusion" on pages 398 – 403 of my report:

1. The Principal Investigators have used entry criteria that do not define the population they purport to be studying; they are not studying ME/CFS, but ubiquitous chronic fatigue. The two are not the same, as confirmed by the American Medical Association in July 1990. The PACE Trial Investigators have long desired to investigate the role of psychiatric illness in "chronic fatigue" (ie. in chronic fatigue without organic aetiology). ME/CFS is not a psychiatric illness but a classified neurological disorder, just as multiple sclerosis is a classified neurological disorder. Further the PIs' failure to recognise the importance of subgroups only compounds this basic flaw. **You do not attempt to address this cardinal concern.**
2. 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. It should never be suggested to trial participants that the intervention they are undertaking is a cure unless it is certain that it is indeed curative, in which case there would be no need for a clinical trial to prove the efficacy of the intervention. **You dismiss this concern by stating: "I should make it clear that MRC considers it good practice for researchers to engage with trial participants". Your comment fails to address my concern that such engagement should not be specifically directed at achieving the desired outcome of the trial by publishing and promoting glowing reports from trial participants during the trial and by invoking trial participants to praise the trial to their friends and contacts and to influence and encourage those contacts also to enter the trial. To do so is unethical, but that is what happened in the PACE Trial.**
3. The PIs propose to carry out a secondary analysis of the data by using criteria that do not officially exist (the "London" criteria) as well as the CDC 1994 criteria (which may include psychiatric patients and do not specifically identify patients with discrete ME). If the PACE Trial Oxford entry criteria had been rigorously applied, no amount of secondary analysis would identify those with ME. **You do not address this concern.**

4. The Investigators diluted the entry criteria after the PACE Trial had commenced by moving the SF-36 (physical function score) goalposts and by including people who had previously undergone CBT/GET and had initially been rejected as PACE Trial participants. It cannot be denied that the PACE Trial Investigators changed the design of the Trial as they went along, which must surely undermine the reliability of all conclusions to be drawn from the data, not least because the first tranche of participants met different entry criteria from those who were recruited later. This can only mean that, because the entry criteria had been diluted, people in the second and subsequent tranches were less ill and are thus more likely to respond favourably to the interventions. **You do not address this concern.**

5. The Investigators failed to take account of the extant literature about the disorder in question, which is a very serious issue in a clinical trial. **You do not address this concern.**

6. The Investigators mis-portrayed ME/CFS as a dysfunctional belief instead of a chronic inflammatory neuroimmune disorder. **You do not address this concern.**

7. Even though they acknowledge they do not know what causes “CFS/ME”, in the CBT and GET arms of the trial the PIs assumed that participants have no physical disease. The PIs, however, did not inform participants of this and portrayed their own assumptions as established facts, thereby deliberately misleading participants. **You do not address this concern.**

8. The Investigators did not include essential objective pre-trial or post-trial cardiovascular or immunological screening. **You do not address this concern.**

9. The Investigators chose a six minute walking test as “*an objective outcome measure of physical capacity*”. The reference provided by the PIs for this is Buckland RJA et al (BMJ 1982:284:1607-1608) but the paper itself cites McGavin CR et al (BMJ 1976:i:822-823), which draws attention to the difficulty of achieving reproducible results with such a test. Moreover, the Chief Principal Investigator himself, Peter White, has published evidence supporting the need for serial post-exercise testing (Immunological changes after both exercise and activity in chronic fatigue syndrome: a pilot study. White PD, KE Nye, AJ Pinching et al. JCF 2004;12 (2):51-66). **You do not address this major concern.**

10. The Investigators originally intended to obtain a non-invasive objective measure of outcome using post-treatment actigraphy but abandoned this on the spurious grounds that wearing such a

monitor for one week would be too great a burden at the end of the trial (<http://www.biomedcentral.com/1471-2377/7/6/comments>). Therefore, after spending millions of pounds of public money and involving hundreds of people in an intensive regime, the PIs completely fail to obtain objective measurements that would reveal whether or not the interventions are successful in the chosen cohort (who may not necessarily have ME/CFS, since the Oxford entry criteria exclude those with neurological disorders). **You do not address this concern.**

11. The PACE Trial results are to be based only on participants' subjective responses to questionnaires. This is of particular concern when two of the interventions being tested (CBT and GET) specifically encourage participants to re-interpret their symptoms as not resulting from disease but as normal responses to exercise in deconditioned people. **You do not address this concern.**

12. The PACE Trial Investigators did not disclose important information, for example, their own conviction that the participants do not have a physical disease, and their own assumption that two of the interventions, CBT and GET, do not work from a pathological perspective, only from a psychiatric perspective. This could mean that participants were not in a position to provide fully informed consent. The Investigators already know (as does Professor Simon Wessely, who oversees the PACE Trial Clinical Unit) that: "*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). **You do not address this concern.**

13. The PACE Trial manuals describe behaviours and techniques that should not -- and I believe cannot -- be considered ethical by any independent and reasonable observer. Much of the written information and instruction to therapists and doctors appears highly exploitative, as well as revealing an ignorance of ME/CFS. **You do not address this important concern.**

14. The Investigators may not have achieved the required clinical equipoise of the trial because they have already formed their opinion that "CFS/ME" is a somatoform disorder. **You do not address this concern.**

15. The Investigators and some members of the Trial Steering Committee initially failed to declare significant financial conflicts of interest. **You comment about this issue that I made clear in my report that the PIs declared their conflicts of interest in the PACE Trial protocol, whereas I had pointed out that at the Trial Steering Committee meeting on 22nd April 2004, all members present were asked to declare any conflict of interest. No financial conflicts of interest were declared and it was agreed that no-one present had any other substantial or material conflict relevant to their work on the PACE Trial. Amongst those present were Professors Peter White, Michael Sharpe and**

Trudie Chalder, who all work for the health insurance industry and who thus have considerable conflicting financial interests.

No meaningful analysis of a trial with such a heterogeneous cohort is possible. Importantly, the results of the PACE Trial can do little for people with ME/CFS because the trial is based on a myth that is allowed to masquerade as science.

Furthermore, how can the results of an intervention in any trial be “evidence-based” for efficacy in a disorder when those most severely affected by that disorder are excluded from the outset?

You will no doubt be aware that the American Psychiatric Association is intent on including in DSM-5 a catch-all category for somatoform disorders that will include virtually every established medical disorder that causes somatic symptoms “*of unclear pathology*”, thus bringing in millions of organically sick patients under the mental health banner. The APA is indulging in what has been described as “*a seriously unjustified power grab*” and psychiatry “*is becoming much too closely aligned with and mutually reliant on both state and corporate interests as opposed to the interests of the patient*” (Co-Cure ACT: 22nd January 2011). This situation is certainly deemed by me and by many others to be exemplified in the PACE Trial.

To quote Sir Paul Nurse (Nobel Laureate): “*We need to leave the politics and ideology behind and concentrate on the science*”, a view with which the MRC apparently sees no need to concur, since rational argument and extensive evidence have been put in place but which the MRC seems unable or unwilling to comprehend.

Objective evidence is the essence of science so, mindful of your own presentation on 4th December 2009 (“Tackling Fraud in Biomedical Research – An MRC Perspective”) at the Workshop on Mechanisms of Fraud in Biomedical Research II at The Wellcome Trust Centre for the History of Medicine, I find it remarkable that you remain unperturbed about what I and others deem to be abuse of the scientific process throughout the PACE Trial when direct evidence of that abuse has been brought to your attention and when you have had eleven months in which to consider it.

Your failure to address key concerns does indeed bear out the evidence that I put before the Minister, namely, the evidence that the MRC has no intention of heeding the many justifiable complaints that were sent in about the PACE Trial, including those submitted by the ME Association and other ME/CFS charities, clinicians and medical scientists, all of which were apparently systemically disregarded and often not even acknowledged; indeed, Elizabeth Mitchell, the MRC’s External Communications Manager, actually informed one medical scientist (himself a former MRC

grant-holder) who lodged a formal complaint about the PACE Trial via his MP that the MRC had no interest in complaints about the PACE Trial. It appears that, despite considerable evidence-based efforts to persuade it otherwise, the MRC Neurosciences and Mental Health Board remains resolute in its determination to categorise ME/CFS as a somatoform disorder and consequently has no interest in finding – or even seeking --a cure.

You attempt to justify the MRC's funding of the PACE Trial by stating: *“there was a lack of high quality evidence to inform treatment of CFS/ME and in particular on the need to evaluate treatments that were already in use and for which there was insufficiently strong evidence from random controlled trials of their effectiveness”*.

That is a remarkable admission, since the NICE Clinical Guideline 53 of August 2007 relies upon the pre-PACE Trial “evidence-base” to recommend the use of CBT and GET nationally as the intervention of choice for ME/CFS, yet you state in your letter that there was insufficient evidence for the implementation of this nationwide programme of CBT and GET recommended by NICE in its Clinical Guideline 53.

In other words, on the one hand Professor Peter White was strongly promoting CBT/GET in his submissions to NICE because he asserted that there was sufficient evidence of their efficacy for their implementation across the nation, yet on the other hand he has received millions of pounds of tax payers' money to carry out the PACE Trial because there was NOT sufficient evidence of the efficacy of the same interventions.

This can only mean that since August 2007 NICE has been promoting interventions and subjecting sick people throughout the nation to a regime for which insufficient evidence exists, a situation that raises yet more legal issues and ramifications, since the correct option for NICE pending the outcome of the PACE Trial was to have recommended the use of CBT and GET “only in research”, not to have issued recommendations for widespread clinical use when evidence of efficacy for those interventions was insufficient at the time the Guideline was published. This raises the issue of exactly why the Guideline Development Group was so determined to implement nationwide CBT and GET on an insufficient evidence-base.

The evidence that behavioural modification techniques have no role in the treatment of ME/CFS is already significant and has recently been confirmed yet again by a study in Spain, which found that in (ME)CFS patients, the two interventions used in the MRC PACE Trial, CBT and GET, did not improve HRQL (health-related quality of life) scores at 12 months post-intervention and in fact resulted in worse physical function and bodily pain scores in the intervention group (Nunez M et al; Health-related quality of life in patients with chronic fatigue syndrome: group cognitive behavioural

therapy and graded exercise versus usual treatment. A randomised controlled trial with 1 year follow-up. Clin Rheumatol 2011, Jan 15: Epub ahead of print).

To those of us who actually know and who possess written evidence of what has been happening in the PACE Trial, it seems irrefutable that the commercial interests of the health insurance industry (and the PIs who work for it) and of the State far exceed the interests of the patients, a situation which the MRC apparently supports and which calls to mind the words of a famous American lawyer and author: *"They had invested far too much to question their own theories and actions"* (The Confession; John Grisham).

However, it will not be long before the PIs and those who support them will be compelled to acknowledge the iatrogenic harm caused by their pseudo-science and their denial of the biomedical science that underpins ME/CFS. Not only is there increasingly strong evidence forthcoming from the US of a retrovirus being associated with ME/CFS, but privately-funded UK research by ME Research UK (MERUK) carried out in Dundee has uncovered important cardiovascular abnormalities in ME/CFS, including increased oxidative stress leading to damaged blood vessels, abnormal acetylcholine metabolism (an important neurotransmitter and dilator of blood vessels), increased apoptosis which indicates active inflammation, and evidence of arterial stiffness in both adults and children with ME/CFS. Taken together, these findings provide evidence of a compromised cardiovascular system and of significant inflammation in the disease process in ME/CFS patients. Yet more research funded by MERUK has enabled Professor Julia Newton from Newcastle to provide evidence of autonomic nervous system dysfunction in three-quarters of patients tested (and when the ANS goes wrong it results in severe consequences, since it controls cardiovascular, respiratory and digestive function and regulates events in exercising muscle). Additionally, she has shown by MRS a significant impairment of proton excretion following exercise in ME/CFS patients, meaning that patients have delayed recovery from exercise, with dysregulation of acid transporter pathways and vascular flow in muscle (giving rise to the classic post-exertional fatigability in ME/CFS).

It defies credibility to believe that indoctrinating such patients into accepting that they do not have a serious organic illness (but are simply deconditioned and victims of their own aberrant thoughts and beliefs) can help them in any way whatsoever and, since patients quickly work out for themselves that in order to survive they have no alternative but to pace themselves, it does not need a £5 million study to prove that pacing is helpful. The Chief Principal Investigator, Professor Peter White, holds views on pacing that are well-known: *"The theoretical risk of pacing is that the patient remains trapped by their symptoms in the envelope of ill-health"* (Postgraduate Medical Journal 2002:78:445-446). Professor White's published views are incongruous with the stated aim of the PACE Trial.

In reality, "adaptive pacing therapy" (APT) as used in the PACE Trial is little different from GET since it involves achieving and sustaining "targets"; it seems that the Trial Investigators were seeking to

placate participants by referring to APT as “pacing” (which participants know to be helpful) when in reality APT is a vehicle for incremental aerobic (or, according to the Investigators, “paced”) exercise.

In relation to my concern that the objective of the PACE Trial was to reduce the number of patients with ME/CFS on State benefits and to reduce payments by insurance companies, you state: *“Any externally-driven motivation in the decision to fund this trial was a wish to respond to the concerns of patients, carers and doctors that more research into CFS/ME was required”*. **You do not address this concern adequately. Where is the evidence of patients and carers calling for more research into behavioural interventions in ME/CFS? On the contrary, the ME Association called for the PACE Trial to be stopped. Furthermore, why were participants to be questioned about their financial situation and asked about what State benefits they were receiving, including being questioned to ascertain if they were expecting to receive any payment from any insurance policy, with their answers being recorded? Such detailed probing into participants’ financial situation is highly unusual in a clinical trial and is possibly illegal.**

In your letter, you state that experts from the MRC Neurosciences and Mental Health Board who assessed the quality of the research were satisfied that the design was *“of high quality”*; that the MRC reviewers and Research Boards were *“satisfied with the science”* and that the various research ethics committees that approved the trial design were *“satisfied with the ethical aspects”*. **The evidence that was put before you suggests that your reply is a travesty of the truth.**

You state that the Data Monitoring and Ethics Committee (DMEC) was *“independent”*. **You were provided with evidence that at least one member of this three-member committee and members of the Trial Steering Committee were far from “independent”**. Professor Tom Sensky, for example, believes that ME/CFS is a somatoform disorder and he is on record as stating on 10th December 2004 at the launch of the Psychological Medicine Network that (ME)CFS patients lack stoicism and that they transgress the obligations of the sick role. **The evidence is that the committee members came from one school of thought only, this being that ME/CFS is a somatoform disorder.**

You acknowledge in your letter that *“serious adverse events were also reported to the Multi-Centre Research Ethics Committee (MREC) on a regular basis”*, but you pass responsibility for the continuation of the PACE trial onto the DMEC, saying: *“the fact that the DMECs have the responsibility to recommend stopping the trial if patient safety is compromised and did not do so in this case suggests that there was no significant evidence that the interventions were harmful while the trial was running”*. **You do not address the issue of who bears responsibility for any accrued harm and lengthy relapse once the trial has stopped, or the fact that participants were obliged to sign a disclaimer, so if they became house- or bed-bound as a result of the PACE Trial, they would have no means of redress.**

Your letter continues: *“if this study had not been judged to be scientifically excellent and worthwhile, the money would have been spent on other research”*. **It is within my knowledge that, despite being supported by some MRC reviewers, numerous high quality biomedical research proposals on ME/CFS submitted by researchers of the highest calibre were consistently rejected by psychiatrist reviewers from the Mental Health Board. I am therefore convinced that it is not a question of the excellence of the science at all, but of the prevailing bias of the psychiatric lobby who control the Mental Health Board and thus control research on ME/CFS.**

Other issues that you have failed to address include the fact that the PACE Trial seems not to have adhered to the Declaration of Helsinki, for example, the PACE Trial was not based on a thorough knowledge of the existing scientific literature, which was simply ignored or dismissed; participants' confidential data was not kept securely and was stolen but participants were not informed of this, and participants were not informed of the potential adverse consequences of aerobic exercise, all of which breach the Declaration of Helsinki with which the MRC is obliged to comply.

It cannot be reiterated enough that many people – including patients with ME/CFS, their families, academics, medical scientists, informed clinicians and senior politicians including the Deputy Prime Minister – are deeply dismayed by the apparent abuse of the scientific process that seems to have been perpetrated by the MRC itself, by the Principal Investigators and indeed by all those involved with the PACE Trial and also by NICE.

Wessely School psychiatrists are not neurologists, immunologists, neuroendocrine, vascular medicine, or nuclear medicine experts, all of which are outside their area of expertise, so how do they justify their involvement with -- and catchment of -- patients whose disease processes affect multiple organs and systems, given that psychiatrists are not qualified to investigate or explain complex organic diseases for which there is as yet no definitive diagnostic test?

As I pointed out in my report, It is salutary to recall the words of the Presiding Officer (Speaker) of the Scottish Parliament delivered at the ME Research UK international research conference on 25th May 2007 in Edinburgh; Mr Alex Fergusson MSP said he had been contacted by a constituent asking for help: *“She’s had ME for some time and been refused Disability Living Allowance and the State support that comes along with that on the grounds that whilst she has been recognised as having ME, she has not sought or been given psychiatric treatment. **Now that to my mind absolutely sums up the principal concerns of the Scottish Cross Party Group on ME, which is that the cold grip of psychiatry is still far too deeply rooted in the world of ME**”*. The numbers of such cases in the UK are incalculable.

This reply to your wholly inadequate response to my complaint merely re-visits some of the concerns set out in that complaint which you have not addressed and does not consider issues which will be addressed once the PACE Trial results are published.

Finally, I mention a forthcoming documentary about ME/CFS (***Voices from the Shadows***, produced by Josh Biggs and Natalie Boulton, in which I am privileged to feature). In this documentary, which is intensely moving and profoundly disturbing, Professor Leonard Jason (speaking in the UK) is blunt, stating: “*We have a national catastrophe on our hands*”. Indeed so, and it is a catastrophe to which the MRC should be deeply ashamed to have contributed.

Please direct any replies to this letter to my home address above.

Yours sincerely

Malcolm Hooper

Copied by email to Dr Morven Roberts, Trials Portfolio Manager, MRC

Copied by email to The Rt Hon David Willetts MP, Minister of State for Business, Innovation & Skills