Dear [Name],

Freedom of Information request: GRC G0200434 THE PACE TRIAL - ref UKRI – 2018/0073 M

Thank you for your Freedom of Information request submitted on the 30th June 2018 in which you requested the following:

Your Request:

This request concerns the MRC-funded 'Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial', GRC reference G0200434.

Please would you provide the following:

Copies of any and all correspondence between Dr Frances Rawle and Prof Malcolm Hooper regarding the PACE trial, including though not confined to her letter of 6th January 2011 as quoted here.

Our response:

I can confirm that UK Research and Innovation does hold the information that you have requested. Our response is detailed below:

The Medical Research Council (MRC), which is part of UK Research and Innovation, has identified correspondence relating to Professor Hooper's report on the MRC funded PACE Clinical Trial. Copies are attached as listed below:

- UKRI FOIA 2018-0073 Letter 1 from Professor Hooper to the MRC (300310): This letter was addressed to Dr Morven Roberts, however Dr Rawle, as Head of Governance and Policy, provided the response.
- UKRI FOIA 2018-0073 Attachment to Letter 1 ‘Magical Medicine: How to Make a Disease Disappear
- UKRI FOIA 2018-0073 MRC response to Professor Hooper (060111)
A small amount of information has been redacted from Professor Hooper’s second letter and the MRC’s response under Section 40(2) of the Freedom of Information Act, the exemption for personal information.

If you have any queries about this response please contact me, or if you are unhappy with the service you have received in relation to your request and wish to request a review of our decision, please write to:

**Complaints Officer**
UK Research and Innovation
Polaris House
North Star Avenue
Swindon
SN2 1FL
Email: foi@ukri.org

Please quote the reference number above in any future communications.

If you are still not content with the outcome of the review, you may apply to refer the matter to the Information Commissioner for a decision. Generally, the ICO cannot make a decision unless you have exhausted the review procedure provided by UKRI. The Information Commissioner can be contacted at:

**Information Commissioner**
Wycliffe House,
Water Lane
Wilmslow
Cheshire
SK9 5AF

Enquiry/Information Line: Between 9am and 5pm Monday to Friday 0303 123 1113 or 01625 545745. Further information about the Office of the Information Commissioner can be found at [http://www.ico.gov.uk/](http://www.ico.gov.uk/)

Yours sincerely,

UK Research and Innovation, Information Governance Team
Email: foi@ukri.org
30th March 2010

Chief Scientific Adviser to the Gulf Veterans' Association
President: the National Gulf War Veterans and Families Association, NGVFA, (2002)

Dear Dr Roberts,

re: MRC PACE Trial

You will doubtless be aware from Lord Drayson (the Minister with responsibility for the MRC) that on 11th February 2010 I lodged a formal complaint with him about the PACE Trial (reference 2010/0013270POLD).

There were three reasons for going directly to him instead of to you in the first instance, as would have been customary:

1. In response to a formal complaint made in November 2004 by an alpha-rated former MRC grant-holder, and despite the involvement of the then Science Minister, Lord Sainsbury of Turville (reference SAMP001/040728) and Dr Rudi Vis MP, the MRC External Communications Manager, Elizabeth Mitchell, had already made plain that the MRC is not interested in considering complaints about the PACE Trial.

2. By lodging a complaint with the MRC Clinical Trials Manager, we are mindful of the fact that the person intimately involved with the PACE Trial, Professor Simon Wessely, is in charge of the PACE Clinical Trial Unit.

3. Given that the MRC is co-funding the PACE Trial, inviting the MRC to consider this substantial complaint would seem to be inviting the MRC to be both judge and jury in its own court – hardly consistent with the most elementary standards of independence and justice.

However, following the advice of Lord Drayson, a copy of "Magical Medicine: how to make a disease disappear" is enclosed, which sets out our concerns in detail.

Many members of the international research community are monitoring the PACE Trial particularly in the light of –
The total failure to engage with the vast body of significant biomedical evidence about the nature of ME/CFS contained in more than 4,000 published, peer-reviewed research papers.

- The misleading and contradictory content of the Trial manuals demonstrating the apparent coercion, and exploitation of patients.
- The seriously flawed and inadequate science that underpins the Trial.

We have taken much time and great care in compiling the evidence presented in ‘Magical Medicine’ and I look forward to receiving your reasoned response to our legitimate concerns expressed therein.

I would, therefore, appreciate an informed and considered reply and not the standard and dismissive MRC proforma letter that has been sent to many people who have already written expressing their concerns about the inadequacy of the PACE Trial.

Yours sincerely

*Malcolm Hooper*

Enc. “Magical Medicine: how to make a disease disappear.”

Dr Morven Roberts
Clinical Trials Manager
MRC
20 Park Crescent
London
W1B 1AL

[Web download]
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. JCFS 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 insufficient 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
Dear Professor Hooper,

I am writing in response to your letter addressed to Dr Morven Roberts earlier this year and the accompanying document “Magical Medicine: how to make a disease disappear”. I apologise for the delay in replying - it has taken us some time to get to grips with the content of your very lengthy document and understand fully the nature of your assertions and the evidence you have provided to support them. Your letter to Dr Roberts implies that you wish us to focus our response on concerns relating to the PACE trial. From our reading of your report, it appears that the main concerns you raise in relation to the trial, and the involvement of the MRC, are as follows:

1. That the MRC should not have funded the trial because the trial design and the science behind it were flawed, the decision to fund the trial was politically motivated, and that the trial itself was a waste of money.

2. That one or more of the interventions being tested might be harmful to participants, and that there was a high incidence of serious adverse events

3. That investigators and clinicians involved in the trial have used unethical means to encourage patients to participate in the trial, and to stay in the trial once recruited, including misrepresentation that amounts to coercion and exploitation of vulnerable patients

I will deal with these points in turn.

1. MRC funding of the PACE trial.

The MRC’s decision to fund this trial was based on the fact that there was a lack of high quality evidence to inform treatment of CFS/ME, and in particular on the need to evaluate
treatments that were already in use and for which there was insufficiently strong evidence from randomised controlled trials to support their effectiveness. The decision to fund this trial was based on MRC’s usual rigorous peer review process for clinical trials, involving written reviews from experts and then review by the Neurosciences and Mental Health Research Board to assess the quality of the research proposed. These experts were satisfied that the design put forward was of high quality, would provide useful evidence to help doctors and patients decide whether any of the four treatments to be evaluated was likely to be worth pursuing, and would inform decisions on the provision of treatment by the NHS. You consider that the scientific basis of the study was flawed because the interventions evaluated reflected the view that CFS/ME is a psychological condition, and raise a number of criticisms regarding the entry criteria and the measures used to define outcomes. The MRC reviewers and the Research Boards were satisfied with the science; the various research ethics committees that approved the trial design were satisfied with the ethical aspects. The trial has been overseen throughout by both an independent expert steering group and an independent Data Monitoring and Ethics Committee. The randomised trial design should show whether or not the interventions have any beneficial outcome for patients, whatever the possible cause of the illness. In this case, there was preliminary evidence that the treatments to be tested had some effect. The criticism in your document that the trial is not properly randomised because the patients were assessed for eligibility before entry into the trial seems to be based on a misconception that a randomised trial means that patients are randomly selected for entry. In fact, the term randomised when applied to clinical trials relates to the process for allocating patients to treatment or control groups to avoid bias, not the process for inviting patients to participate in the trial.

In the document you assert (pp 303 and 313) that the objective of the trial was to reduce the number of patients with CFS/ME on state benefits and reduce payments by insurance companies, but this was certainly not the MRC’s objective in funding the study, nor was it a stated objective in the protocol. The MRC’s objectives, as laid out in our Royal Charter, are to fund high quality research that leads to improvements in human health. We would of course hope that our research will result in people being healthier and fewer being in the unfortunate position of being incapable of working due to ill health, but this is not a primary consideration in individual funding decisions. 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 have also suggested that this trial was a waste of public money that would have been better spent on research on the aetiology of the disease. The two are not mutually exclusive and, while understanding the cause of the condition is obviously important, if there are potential treatments available, it is equally important to test their effectiveness
quickly, so that they can be introduced into service without undue delay if they prove
effective. Of relevance to this, the PACE trial was testing adaptive pacing therapy, which
had not previously been tested in a large trial, and which was particularly supported by
patient organisations. I should add that MRC rarely earmarks money for research on
specific diseases, and certainly did not have an earmarked budget for CFS/ME at that
time. If there had been proposals of sufficient quality relating to disease aetiology, they
would have been funded too, and if this study had not been judged to be scientifically
excellent and worthwhile, the money would have been spent on other research. Whether
the money for the trial proves to have been well spent will of course depend on the
outcome of the trial, which is not known yet, but the independent trial steering
committee have recommended the continuation of the trial at all of their meetings.
Three of the treatment interventions tested are expensive to deliver so evidence of a lack
of effectiveness for any of these treatments would not necessarily mean that the money
spent had been wasted, as redirection of NHS resources currently used for interventions
shown to be ineffective would be a worthwhile outcome for a trial.

2. Potential harmful effects of interventions
The PACE trial was overseen by an independent Data Monitoring and Ethics Committee
(DMEC), which monitored the outcomes and the incidence of adverse events in all groups
while the trial was in progress and had the responsibility for ensuring patient safety. As
noted in your document, serious adverse events were also reported to the Multi-Centre
Research Ethics Committee (MREC) on a regular basis. Based on some derived figures
you suggest that the incidence of serious adverse events (SAEs) in this trial was high.
The overall incidence of SAEs for each intervention group will not be known until the
results of the trial are published, but the design of the trial includes an analysis of safety
outcomes, including SAEs; the fact that 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.

3. Allegations of misrepresentation and coercion
You allege that in the course of the trial the patients had been misinformed about the
nature of CFS/ME, and the likely effectiveness of the interventions, and that this
misinformation might be construed as coercion. This trial was approved and overseen by
the West Midlands Multi-centre Research Ethics Committee, and I understand that your
complaint was received by the overseeing National Research Ethics Service, who decided
to take no action in this matter. All the NHS ethics committees are completely
independent from the MRC. In approving the trial they have a particular responsibility
for ensuring that information provided to patients is appropriate to ensure consent is
adequately informed. As evidence to support coercion, you point to the fact that the MREC asked for changes in the patient information leaflet on the basis that it might be considered coercive (p231). We understand the MREC’s concern related to the way in which the treatments options for patients at the end of the trial were described. The fact that the committee picked this up suggests they were particularly alert to the need to avoid coercion, and, as you confirm in your document, changes were indeed made to the patient information leaflets which dealt with their concern. We also note that the trial used a two-stage consent process, allowing a week’s consideration between first and second consent, which would make coercion unlikely. You suggest that the acronym for the trial, PACE, itself could be seen as misleading and therefore a form of coercion. Given that one of the arms of the trial was adaptive pacing therapy it would appear to be a reasonable name, and it seems unlikely that patients would be influenced by the name more than by the patient information sheet, which made it very clear what the four arms were. You also suggest that encouraging participants to send in their views on participating in the trial, and publishing positive statements in the trial newsletter for patients, might be construed as coercive. I should make it clear that MRC considers it good practice for researchers to engage with trial participants, to keep them informed about the progress of the trial, and to listen to their views. At the MRC we have received no complaints at all from patients participating in the PACE trial, whether about misinformation, coercion or any other matter. You point to statements published on the internet from one patient in the trial (in the context of a complaint about Action for ME involvement) stating she felt she had been treated badly by the therapist when she withdrew from the trial, but we are not aware of any formal complaint in this matter. Neither have the trial centres received any formal complaints from trial participants suggesting coercion or misrepresentation. One of the safety outcomes the trial will analyse is the proportions of participants who withdraw from treatment.

You assert in a number of places that the Principal Investigators (PIs) have a conflict of interest because of connections with the Department of Work and Pensions and/or the insurance industry. You make it clear, however, (p262), that the PIs declared these potential conflicts of interests in the PACE trial protocol, and in so doing they have followed the expected course of action in relation to the trial. This will no doubt be a matter too for the journal to take into account when the manuscript is submitted for publication.

As you know, the PACE trial has now finished. The data are being analysed and reports are being written; publication of the results is expected in 2011. If one or more of the interventions are shown to be beneficial, this information will be helpful to patients and to the NHS. If, as you clearly believe, the treatments being evaluated are either ineffective or actively harmful, the results of the trial will likely show this. This in itself
would be a valuable outcome of the trial, in that it would be evidence to support the redirection of NHS resources away from ineffective therapy. If, on the other hand, the trial shows that one or more interventions are helpful for some patients, it is to be hoped that this evidence will enable more patients to benefit from this treatment where it is appropriate for them.

In conclusion, and after careful consideration of all your complaints by myself and senior colleagues, I believe that none of your complaints can be upheld, and that your concerns are groundless and without substance. We will therefore be taking no further action in this regard.

I apologise again that it has taken longer than I would have wished to respond to your letter.

Yours sincerely

Frances C Rawle PhD
Head of Corporate Governance and Policy
21 February 2011

Dear Professor Hooper,

I am writing in response to your letter of 26th January. I am sorry you found my earlier letter in response to your complaint about the PACE trial disappointing. It appears that my letter, which I sent to your University address, took some time to reach you. I did send it also by e-mail, but I note that you have changed your e-mail address.

Many of your concerns relate to the aetiology and disease mechanisms of CFS/ME, the disease classification and the diagnostic criteria used, and I cannot comment much further on these issues - the MRC acknowledges that CFS/ME is a distressing and debilitating condition and that not enough is known about the aetiology and mechanisms involved. To help address this we have recently announced the allocation of £1.5m for a call for proposals to encourage more research, focussing on the priority areas identified by the expert group last year, namely:

- Autonomic dysfunction
- Cognitive symptoms
- Fatigue
- Immune dysregulation (eg. through viral infection)
- Pain
- Sleep disorders

Details are on our website at
www.mrc.ac.uk/Ourresearch/ResearchInitiatives/CFSME/index.htm#P80_5718

In deciding to fund the PACE trial, the MRC relied (as it does for any such funding decision) on peer review by clinical and scientific experts in the field, and by experts in the design and conduct of clinical trials. These experts, and the experts on the Research Ethics Committees that approved the trial, were satisfied with the protocol, which lays out the entry criteria and outcome measures to be used. You clearly fundamentally disagree with
these experts, but it is not appropriate for MRC officials to enter into this scientific debate, which is best conducted in the scientific literature. As clearly stated in the protocol, which as you know was published in the open access journal BioMed Central Neurology in 2007, the aim of the PACE trial was to provide evidence about the relative benefits, cost effectiveness and adverse effects of the most widely advocated treatments for CFS/ME. The validity of the trial does not depend on any particular theory of disease aetiology or causation; it was simply designed to show whether the treatments in common use are safe and effective. The trial is now complete and the results have been published in The Lancet [link to article](www.thelancet.com/journals/lancet/article/PIIS0140-6736(11)60172-4/abstract).

You have highlighted specific issues in your lengthy document to which you felt I had not adequately responded, and I will provide what additional responses I can in the order of your numbered paragraphs.

1. In your view the entry criteria used mean that the PACE trial is studying patients who have chronic fatigue and not CFS/ME, and you are concerned that the results might be applied to different patient groups. The clinical and scientific experts who reviewed the protocol were satisfied with the entry criteria, which are clear in the published protocol and are also set out clearly in the published results, so that clinicians and others using the results of the trial to inform their practice will know which patient groups the treatments should be applied to.

2. You state that participants in a clinical trial should not be told how effective the intervention they are receiving is. However, in order that properly informed consent can be obtained, it is normally considered important that participants are told any information that is known about the likely effectiveness (and possible harms) of the treatments being trialled. You express a concern that the motivation for publishing positive comments from participants in the trial newsletter, and encouraging them to let other sufferers know about the trial, was to influence the outcome; I am not in a position to comment on the triallists’ motivation, but it seems unlikely that reading such comments, which did not mention specific treatments, would have a material effect on participants’ health and we do not consider it unethical to publish comments from current participants in order to encourage interest in the trial. All participant newsletters circulated during the trial were considered ethically satisfactory by the MREC before being sent out.

3. As noted above, I cannot comment on the use of particular diagnostic criteria. The independent members of the trial steering committee reviewed and agreed the plans for secondary analysis and those that are to be published will have been reviewed by the expert peer reviewers selected by the journal.

4. I acknowledge that there have been changes to the protocol for the PACE trial since it started. It is not uncommon for minor protocol modifications to be made while a trial is in progress; all such modifications must be approved by the Trial Steering Committee (TSC), the Data Monitoring and Ethics Committee, and the MREC that approved the original protocol, and they were in this case. In addition, the MRC Board was aware of the changes when it agreed to the extension to the original funding period for the trial, so clearly the Board did not consider the changes undermined the trial.
5. The peer reviewers and the MRC Board were satisfied that the PACE trial was adequately justified based on the extant literature when the funding decision was taken. The published protocol refers to two independent systematic reviews of treatment for CFS/ME. In addition, the TSC monitored any new findings emerging in the scientific literature during the course of the trial which could potentially have an impact on the design or rationale for the trial; had any such findings meant that the trial was no longer ethically or scientifically justified then the TSC would have stopped the trial.

6. Neither the patient clinic leaflet nor the PACE trial invitation letter (which provided information on the trial to potential participants), portray CFS/ME as a dysfunctional belief. The clinic leaflet gives information on several possibilities as to the causes of the condition, including infections, immune and hormonal factors.

7. The information given to patients makes it clear that doctors would rule out other physical diseases before diagnosing CFS/ME or offering entry into the PACE trial, but also explains various abnormalities found in patients with a diagnosis of CFS/ME. There is no statement or implication that that there is no physical disease; the patient clinic leaflet says on the front page “In this clinic we believe CFS/ME is a real illness.”

8. You are correct, cardiovascular and immunological screening were not included in the protocol for the pre-trial assessment. However, as mentioned above, doctors carried out a range of medical tests in order to diagnose CFS/ME and rule out other possible causes of the symptoms before patients were offered entry into the trial. These tests included a physical examination and several tests of the immune system.

9, 10 & 11. All these points relate to the outcome measures for the trial. These were judged to be appropriate by the expert clinical and scientific reviewers and by the MREC which approved the protocol; any changes to the original protocol would have had to be approved by the MREC and the TSC.

12. The MRC considers that the views of the principal investigators as to the nature of the disease or the potential mechanism of action of the interventions being tested, or whether these are revealed to potential trial participants, have no bearing on participants’ ability to give informed consent.

13. The PACE trial treatment manuals were reviewed by the MREC which approved the trial.

14. In a clinical trial, the requirement for equipoise relates to the evidence as to the efficacy or effectiveness (in absolute terms and relative to each other) of the interventions under trial, and not to the beliefs of the investigators (or anyone else) regarding the causes of the disease.

15. At the first meeting of a new Trial Steering Committee, the focus is usually on establishing that the independent members, involved with the trial for the first time, have any conflicts to declare, which was the case in this trial. The Principal Investigators are automatically assumed to have conflicts arising from their role, which is why independent
members and an independent chair are required for the TSC. In relation to financial
conflicts, the PACE PIs have repeatedly declared the potential conflicts arising from their
having had consultancies with the DWP or insurance companies. The MRC, and the
Research Ethics Committees, took the view that these links did not compromise their ability
to run the trial. In order to avoid bias in the results, the statistician who analysed the main
trial data was blinded as to the treatment allocation of the four groups of patients.

I cannot comment on the NICE guidance; any concerns regarding the development of this
guidance should be taken up with NICE directly.

You ask why questions relating to the participants’ financial situation were included in the
pre-trial assessment. We accept that this is unusual in a clinical trial but, as is clear from
the published protocol, being in receipt of a disability pension was amongst a group of
factors found in previous work to be potential predictors of a negative response to
treatment. The inclusion of financial questions was therefore made part of the investigation
into predictors of outcome. The other reason to include financial questions was to be able
to measure how treatments affected both healthcare costs and costs to society. It was
made clear in the patient invitation letter prior to recruitment that such questions were
included, so that patients not willing to answer could decline to participate.

The MRC does not believe that the beliefs regarding the aetiology of CFS/ME materially
affect the ability of members of the Data Monitoring and Ethics Committee to act
independently, since data provided to the DMEC were blinded as to treatment allocation.

I acknowledge that there was unfortunately one instance of a breach of security during the
PACE trial, when one recording containing confidential patient information was stolen from
within a hospital, having not been kept sufficiently secure. Security procedures were
changed after this incidence and we are not aware of any further problems.

You allege that the MRC Neurosciences and Mental Health Board (NMHB) has behaved in a
biased fashion and has been “controlled” by psychiatrists in their funding decisions
regarding applications for research into CFS/ME. I cannot provide specific evidence to prove
otherwise, since Board discussions are confidential. However, all the MRC Boards take
collective responsibility for their funding decisions, all members take an active part in
decision-making, all members are required to act according to the seven principles of public
life (the Nolan principles), and the Board Secretary (a member of MRC office staff) and the
Chair are required to ensure that decision-making processes are fair. The membership of
NMHB covers the full range of expertise in neuroscience and mental health, and only a small
proportion of members are psychiatrists at any one time, so it is unlikely they could control
the outcome of decisions. It is true to say that the many applicants whose applications are
declined (around 80%) are rarely happy with the decision, whatever the Board or panel
involved, and some would rather believe that the process is flawed than accept that their
application did not reach the competitive standard. Some revise their applications taking
into account the comments from peer reviewers and the Board and are subsequently
successful in obtaining funding from MRC or another funding body.
I have responded as fully as I can to your concerns. However, it is clear that many of the points on which you consider my earlier response inadequate relate to scientific disagreements on which I cannot comment further.

If you are not satisfied with how I have handled your complaint, you may choose to refer it to the MRC Complaints Officer, in accordance with stage 2 of MRC’s formal complaints procedure, detailed on our web site at www.mrc.ac.uk/About/Informationandstandards/Complaints/index.htm. Please note, however, that the complaints procedure specifically excludes complaints which amount to a disagreement with the scientific decisions made by MRC Boards, Panels and other Committees. I should point out that since the Complaints Officer is a member of my team within Head Office, she would necessarily refer any formal complaint to another senior member of staff in a different department.

Yours sincerely

Frances C Rawle PhD
Head of Corporate Governance and Policy