Sent on behalf of Malcolm Hooper, Emeritus Professor of Medicinal Chemistry,

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Matthew Wicks
Private Secretary to the Rt Hon David Willetts MP
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1, Victoria Street
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5th January 2011

Dear Matthew

I do hope you had an enjoyable break over Christmas and I wish you a happy New Year.

Further to my last email of 23rd December 2010 about Professor Hooper's complaint about the MRC PACE Trial, he has requested that I ask you to put the following points before the BIS officials who are dealing directly with the MRC about it, and that those BIS officials request and obtain a prompt response from the MRC about the eight specific points below.

1. The MRC's complaints procedure gives its own definition of a complaint as:

a) "*an expression of dissatisfaction, however made, about the standard of service, actions or lack of action by MRC Head Office"*

b) it lists *"unreasonable delay in answering a query"* as an illustration of what it regards as a legitimate complaint

c) its complaints procedure further states: *"At the MRC, we work hard to ensure that you have a positive experience when you contact us, and try to resolve your queries promptly and courteously"*

d) notably, it also states: *"Your complaint will be acknowledged immediately and you will be given a timescale for our full reply"*

e) it further states: "*All complaints will be thoroughly investigated and you will be sent a full written response normally within 20 working days of your complaint being received"*

f) It continues: "*If, however, we are unable to send a final response within that timescale, we will send you an interim reply telling you why and when you may expect to know the outcome"*(http://www.mrc.ac.uk/About/Informationandstandards/Complaints/index.htm).

It is eleven months since Professor Hooper's complaint was first lodged. The MRC has failed on each of its own above criteria.

2. We have 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.

3. A substantive amount of scientific evidence has accumulated about the chronic inflammatory nature of ME/CFS both before and during the lifetime of the PACE Trial, some of which was reported by the PACE Trial Chief Principal Investigator (Professor Peter White) himself in 2004 before the PACE Trial began recruiting participants (JCFS 2004:12 (2):51-66). In that article, White et al stated:

"We designed this pilot study to explore whether the illness was associated with alterations in immunological markers following exercise. Immunological abnormalities are commonly observed in CFS*…Concentrations of plasma transforming growth factor-beta (TGF-b) (anti-inflammatory) and tumour necrosis factor-alpha (TNF-a) (pro-inflammatory) have both been shown to be raised….Abnormal regulation of cytokines may both reflect and cause altered function across a broad range of cell types…..**Altered cytokine levels, whatever their origin, could modify muscle and or neuronal function.***

"*Concentrations of TGF-b1 were significantly elevated in CFS patients at all times before and after exercise testing.*

"We found that exercise induced a sustained elevation in the concentration of TNF-a which was still present three days later, and this only occurred in the CFS patients.

*"**TGF-b was grossly elevated when compared to controls before exercise** (and) showed an increase in response to the exercise entailed in getting to the study centre.*

"These data replicate three out of four previous studies finding elevated TGF-b in subjects with CFS.

"The pro-inflammatory cytokine TNF-a is known to be a cause of acute sickness behaviour, characterised by reduced activity related to 'weakness, malaise, listlessness and inability to concentrate', symptoms also notable in CFS.

"These preliminary data suggest that 'ordinary' activity (ie. that involved in getting up and travelling some distance) may induce anti-inflammatory cytokine release (TGFb), whereas more intense exercise may induce pro-inflammatory cytokine release (TNF-a) in patients with CFS".

No objective pre- or post-exercise measurement of participants' immune system function was built into the PACE Trial.

The existence of such evidence illustrates the serious failure of the MRC to ensure that rigorous scientific principles are observed in all research projects it funds, particularly the requirement for studies to use well-characterised cases.

At the time of application there were already several thousand published biomedical papers which clearly demonstrated that the premise upon which the PACE Trial was predicated was scientifically unsustainable. Many of these papers were sent to the MRC by concerned members of the ME community but were disregarded and the existing evidence-base about ME/CFS was simply ignored.

It is troubling to observe how the MRC appears to condone the extent to which the Principal Investigators seem to have allowed their unassailable belief that ME/CFS is a behavioural disorder to undermine the objectivity of the PACE trial.

The MRC's funding of the PACE Trial is all the more puzzling in light of its own list of ME/CFS papers from January 2004 – June 2009 on its website, many of which show ME/CFS not to be a behavioural disorder (http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC006509). How on the

one hand can the MRC justify funding a trial that is predicated specifically on disabusing participants of their belief that ME/CFS is an organic disorder whilst on the other hand its own website lists published research papers confirming ME/CFS as an organic disease?

4. The MRC itself appears to regard people with ME/CFS with disdain approaching contempt (see Appendix 1 to Professor Hooper's complaint, for example: ***"The Unit's scientists must remain wary of patient-pressure groups. Tony Johnson's work on chronic fatigue syndrome (CFS), a most controversial area of medical research, has had to counter vitriolic articles and websites maintained by the more extreme charities and supported by some patient groups, journalists, Members of Parliament, and others, who have little time for research investigations"***). This disparaging view, for which ample evidence exists, has prevailed throughout the MRC for many years.

Mindful of this, Professor Hooper's concern about the implications of the PACE Trial for ME/CFS patients led him to lodge a formal complaint with the West Midlands MREC (Multicentre Research Ethics Committee) whose members had granted ethical approval for the PACE Trial on 24th October 2004.

This ethics committee approval was granted even though the design of the Trial did not accord with the elementary research requirement for as homogeneous a cohort as possible in a clinical trial (ie. it intentionally included those who do not suffer from the disorder allegedly under investigation, substantial evidence of which exists).

Of cardinal concern was the fact that the Trial entry criteria (ie. the Oxford criteria: JRSM 1991:84:118-121) do not include those with the pathognomonic symptom of ME/CFS (post-exertional fatigability with malaise) but select those with chronic "fatigue" and persistent tiredness, which bear no relationship to post-exertional fatigability (indeed the Oxford criteria suggest those with neuromuscular disease be used as controls), yet the Principal Investigators insist that they are studying those with ME/CFS, a recognised neurological disorder. The Chief Principal Investigator, Professor Peter White, apparently failed to inform the West Midlands MREC of this salient disparity.

Also ignored by the MREC was the fact that the interventions to be used in the PACE Trial were already known to be ineffective for people with ME/CFS (see, for example, JAMA 19th September 2001:286:11). This was a remarkable departure from procedure on the part of the MREC, given that since 1995 it has been established that *"members of ethics committees should proceed on the basis that the question to be investigated has not already been answered….Under these circumstances the trial would be unethical"* (Lilford et al; JRSM 1995:88:552-559).

It is disturbing to note the extent to which, either through dereliction of duty or through being inadequately informed or even misinformed by the Chief Principal Investigator, the West Midlands MREC failed to adhere to Section 9.7 of the Governance arrangements for NHS Research Ethics Committees (2001) that were in place at the time it granted ethical approval.

It is even more troubling that Dr Janet Wisely, Director of the National Research Ethics Service (NRES) which is part of the National Patient Safety Agency that is supposed to protect patients, dismissed Professor Hooper's complaint about the West Midlands MREC, stating on 22nd March 2010: "*In the case of the PACE Trial I have concluded that there is no likely benefit of a more extensive review of the original decision made by the REC because it was a decision made a long time ago and is unlikely to reveal relevant learning points for NRES"*. The purpose of Professor Hooper's complaint about the ethics committee was not to "*reveal relevant learning points"* for future ethics committees, but to secure a re-appraisal of the ethics involved in the MRC PACE Trial, including abandonment of the trial if that was the only way to prevent potential iatrogenic harm being imposed upon those with ME/CFS.

Dr Wisely's letter continued: "*The study is closed for new recruitment and I do not think it appropriate therefore to ask the REC to reconsider the opinion that was made several years ago. What NRES is able to do is to pass on the concerns that have been raised to those with responsibility for the conduct of the trail* (sic) *for their consideration. However, it seems from the correspondence provided that there has been extensive dialogue and exchanges with these relevant parties and I do not feel there is anything NRES can usefully add to these exchanges".*

The exchanges referred to were between Peter White and the MREC -- quite certainly, the MREC wrote to Peter White on a number of occasions expressing concern that the wording of the PACE Trial Patient Information Sheet was potentially *"coercive"*; he argued that it was not, but eventually he agreed to modify the wording. That it should have been deemed by the West Midlands MREC to be*"coercive"* in the first place is disturbing.

5. There is a perception within the ME/CFS community that the MRC is hostile to any research findings that might contradict the PACE Trial's behavioural model of the disease, particularly the association found by experienced and leading US researchers of the gammaretrovirus XMRV (xenotropic murine leukaemia virus–related virus)/MLV (murine leukaemia virus) with ME/CFS.

An example of this can be seen in the relatively fast-tracked study that was co-funded by the MRC and the Wellcome Trust Sanger Institute (Retrovirology, 20th December 2010, 7:111), about which the senior author, Greg Towers, an MRC scientist and Professor of Virology at University College London, said in a press release entitled "Chronic fatigue syndrome not caused by XMRV virus, study shows":*"Our conclusion is quite simple: XMRV is not the cause of chronic fatigue syndrome … All our evidence shows that the sequences from the virus genome in cell culture have contaminated human chronic fatigue syndrome and prostate cancer samples…we know it is not this virus causing it".*

As the New York Times reported in an article by David Tuller on 3rd January 2011 about Towers' press release: *"Other scientists…have sharply criticised such certainty as unwarranted, noting that the Retrovirology papers themselves expressed their findings in more cautious terms"*.

The New York Times article went on to note that Towers' paper did *"not evaluate other strategies beside PCR…for detecting the MLV-related viruses, like testing for an immune response and culturing the viruses in cell lines".*

Nonetheless, Professor Towers' statement led to banner headlines in the UK such as *"ME 'virus' was actually a lab mistake, study says"* (Independent, 21/12/10), *"Scientists conclude mouse virus does not cause ME"* (Guardian, 20/12/10), *"Chronic Fatigue Syndrome Virus Doubt"* (NHS Choices) and *"Study finds contamination in virus link to fatigue"* (Reuter, 20/12/10).

Such is the concern about the potential impact of Professor Tower's statement on future research that nearly 400 people from around the world have signed a petition asking for him to retract it (http://www.ipetitions.com/petition/xmrv/).

It is notable that whilst the international press were critical of Towers' dismissive statement, the UK press accepted it uncritically and reported it in a way that amounted to misrepresentation of the science, and that the press release was posted on SCICASTS (Science and Technology Daily News Feeds), ensuring maximum impact.

A comment on the Science-Based Medicine blog (http://www.sciencebasedmedicine.org/?p=9461) admirably captured the misrepresentation: "*It is interesting, from a political viewpoint, to note how the…hypothesis put forth in the actual…paper became, in the Wellcome Trust's press release, (1) confidently presented as a proven fact rather than a tentative possibility and (2) ENTIRELY about discrediting the proposed links between chronic fatigue syndrome and XMRV…(See if you can find the one reference to prostate cancer in this press release, compared to the way chronic fatigue syndrome*

is discussed). Regardless of how the science proves out in the end, this kind of misrepresentation of their own work by researchers strikes me as highly unethical and irresponsible".

On 1st January 2011 the President of the WPI issued a statement about Professor Towers' press release containing the following:

"*These results have nothing to do with the reality of a disease or the methods used by those who have detected XMRV in the blood and tissue of patients found to be infected".*

Referring to the October 2009 Science paper, the WPI statement notes that it is necessary to use more than one method and that the XMRV positive studies are *"those which have used multiple methods to show that XMRV is a live replicating gamma retrovirus in human blood and tissue samples using the gold standard methods of viral isolation and antibody testing, in addition to PCR.*

"Recent commentary associated with the negative research papers on XMRV, which used only one testing method, claimed that these studies proved that XMRV was not the cause of human disease….What the authors of the 'contamination studies' confirmed is something that most experienced scientists already know; there are risks associated with using PCR if one does not properly control for contamination. They cannot conclude that other research groups had the same problems or that 'XMRV is not the cause of CFS'.

"Most significantly, the recent Retrovirology publications failed to address the most important pieces of scientific evidence of human infection in the previous XMRV studies, including the fact that XMRV positive patients produce human antibodies to gamma retroviruses, XMRV integrates into human tissues, and infectious virus has been cultured from the blood of hundreds of patients with a diagnosis of Chronic Fatigue Syndrome and ME. Humans do not make antibody responses to mouse DNA sequences from contaminated lab experiments.

"Animal studies involving XMRV demonstrate that the virus moves quickly away from the blood to various organs within the body, such as the spleen, lymph nodes, GI (gastrointestinal) *tract, and reproductive organs. This helps to explain why the virus is difficult to detect in blood even as it replicates in the tissues of those infected.*

"…research groups who have been working on XMRV over the past year…understand that novel scientific discoveries, which threaten current dogma, will continue to be challenged until the evidence can no longer be denied.

"WPI's collaborative research projects are revealing the infectious and inflammatory nature of neuro-immune disease, providing strong evidence against the use of CBT and exercise therapy as rational 'treatments' for those who are ill".

Commenting on the negative studies published in Retrovirology, Vincent Racaniello, Professor of Microbiology at Columbia University whose reputation as a retrovirologist is faultless, said -- after careful reflection -- that they do not imply that previously published studies are compromised.

The US researchers used a combination of biological amplification and molecular enhancement techniques to detect XMRV in 67% of ME/CFS patients tested (Lombardi et al; Science, 23rd October 2009), and showed that XMRV in human blood can infect other human cells ("*Cell culture experiments revealed that patient-derived XMRV is infectious and that both cell-associated and cell-free transmission of the virus are possible. Secondary viral infections were established in uninfected primary lymphocytes and indicator cell lines after their exposure to activated PBMCs, B cells, T cells, or plasma derived from CFS patients*"). The US research demonstrated that some people with ME/CFS mount an immune response to XMRV (and if XMRV is the result of contamination, there would be no such antibody response). Furthermore, XMRV was found in 3.7% of the control samples.

As the New York Times article noted, the senior author of the Science paper, Dr Judy Mikovits, observed about the Towers et al paper: *"Nothing that has been published to date refutes our data".*

Furthermore, the Cleveland Clinic's Robert Silverman (an immunologist from the Department of Cancer Biology) had pointed out (Nature News, June 2010) that the failure of other studies to confirm the US findings was not unexpected, since different groups used different techniques and different subjects (so no attempt was made to replicate the US findings).

In August 2010, scientists at the US FDA, the NIH and Harvard demonstrated from their own research that numerous XMRV-like virus sequences (MLV-related viral sequences) were found in 86.5% of patients with ME/CFS and, notably, that these were found in 6.8% of healthy blood donors (Lo, Komaroff, Alter et al; Proc Natl Acad Sci 2010 Sept 7;107(36):15874-9. Epub 2010 Aug 23).

Notwithstanding, the NHS "Choices" website went even further to disparage and dismiss the US findings found by such prestigious establishments as the National Cancer Institute, the Cleveland Clinic, the Whittemore Peterson Institute for Neuroimmune Diseases at the University of Nevada,

the FDA, the NIH and Harvard of a close association of XMRV/MLV with ME/CFS, asserting: "*Well-conducted research has now suggested that this link was made because of lab contamination in earlier research….The newspapers have all reported this story well, emphasising the strength of the researchers' conclusion that ME is not caused by this virus".*

Predictably, the NHS website revealed the institutional bias about ME/CFS that permeates UK medicine by seizing the opportunity to mention the behavioural model, continuing: *"other possible contributing factors include…lifestyle and psychosocial factors".*

Another person in the UK to dismiss the US research was Professor Tim Peto from Oxford (a member of the PACE Trial Management Group), who said on record: "*There have now been a number of attempts which have failed to find the retrovirus in other samples, and this research suggests that in fact XMRV is probably a contamination from mouse DNA. These latest findings add to the evidence and it now seems very, very unlikely that XMRV is linked to chronic fatigue syndrome"* (http://www.bbc.co.uk/news/health-12041687).

Despite the certainty of some MRC scientists that XMRV has no role in ME/CFS, patients with ME/CFS in the UK and many other countries are now banned for life from donating blood because of international concern about gammaretroviral contamination of the blood supply, as infectious virus has been cultured from blood cells of patients with ME/CFS.

Indeed, the world-renowned virologist, Dr Harvey Alter, went on record at the December 2010 meeting of the US Blood XMRV Scientific Research Working Group (which reports to the FDA's Blood Products Advisory Committee) as stating: "*The current evidence for disease association is very strong that XMRV or MLV is strongly associated with (ME)CFS".* He went on to state: "*The truth will out over the next year*".

The outing of that truth can only be hampered by use in the MRC PACE Trial of entry criteria that preferentially select patients whose fatigue is psychogenic and which, on the Chief Principal Investigator Professor White's own acknowledgement and as his own data clearly demonstrate, include subjects with primary psychiatric disorders in a trial that purports to be studying ME/CFS (Sampson DP. Bulletin of IACFS/ME 2010:18:2).

Whilst previous epidemics of "pure" ME are thought by many to have been caused by primary enteroviral infection with Coxsackie B virus, a current working model for the global explosion of ME/CFS is that a retrovirus such as XMRV/MLV may be disrupting the immune system, thus allowing reactivation and persistence of numerous latent viruses Including Coxsackie B virus, previously

thought not to remain in the body but now shown by US research (carried out by Professor Nora Chapman from the University of Nebraska) to remain latent and thus capable of being reactivated if the immune system becomes dysfunctional (for example, by a retrovirus such as XMRV/MLV).

BACME (British Association of CFS/ME), a self-appointed organisation that seems to be accountable only to itself, membership of which is open only to those who support the NICE Guideline CG53 and who accept its recommendation of behavioural therapy and graded exercise in the management of ME/CFS, has taken upon itself the role of training NHS staff according to its members' beliefs. In his summing up of the BACME meeting held in October 2010 at Milton Keynes, the PACE Chief Principal Investigator (Peter White) appeared dismissive about XMRV, declaring that it is probably *"not our future"*, and that the PACE Trial is *"going to be helpful to us. It will inform us about treatments that we use now. Effectiveness and safety will be addressed".*

To continue to dismiss the international evidence on ME/CFS and to support the Wessely School's disproven behavioural model indicates that those involved with the PACE Trial seem to be no longer scientists but ideologues.

This apparent certainty, which is not backed by evidence, could prevent the UK from participating in research in an important emerging field in which, for example, researchers from Cornell University are currently studying the association of XMRV protein expression in the phenomenon of exercise intolerance (the key feature of ME/CFS) and the increases in inflammatory cytokines in relation to the reduced physical ability observed in ME/CFS patients, whilst researchers at the University of Miami are looking at (virally-induced) chronic immune activation and at the evidence that exercise is already known to be sufficient to inflame those pathways even further.

Immune activation and inflammation have long been deemed the principle components in the pathophysiology of ME/CFS and abnormalities in the stress response as a prominent feature of ME/CFS were identified two decades ago by Demitrack et al (Journal of Clinical Endocrinology and Metabolism 1991:73:6:1224-1234). University of Miami researchers Professors Fletcher and Klimas et al have now demonstrated that a key stress mediator (neuropeptide Y) is statistically elevated in plasma from ME/CFS subjects compared with healthy controls and that the acute stress responses shown to occur in ME/CFS represent regulatory mechanisms that are critical to survival. The researchers note that persistence of ME/CFS involves complex interaction of immune, autonomic and neuroendocrine regulation (Behavioural and Brain Functions 2010:6:76: doi:10.1186/1744-9081-6-76), which vitiates the PACE Trial Investigators' belief and assertion that persistence is due to abnormal illness behaviour, aberrant beliefs, dysfunctional thinking and deconditioning, and even less to their accusation of over-vigilance to normal bodily sensations by patients with ME/CFS.

Yet other researchers at Stanford (US) are setting up the Stanford Chronic Infectious Diseases Initiative that includes chronic inflammatory infectious disorders such as ME/CFS, an initiative that already has the support of the Director of the Institute for Immunity, Transplantation and Infection, as well as the Chair of the Department of Medicine.

It is sobering to compare such research with the MRC PACE Trial, and to reflect upon the apparent lack of impartiality with which the MRC has acted to support the behavioural model of ME/CFS, a model that is not based on medical science. Unlike the WPI, which has consistently called for more research on the association of XMRV with ME/CFS, the MRC sweepingly dismisses the potential role of a retrovirus, as well as the earlier, well-founded, biomedical evidence. This is more akin to propaganda and ideology than science.

6. None of the multitude of known biomedical abnormalities can be rectified by behavioural interventions such as those used in the PACE Trial that, far from providing psychological support, are didactic and directed at disabusing patients of their correct belief that they are seriously physically ill.

The international research destroys the scientifically untenable notion of the MRC PACE Trial psychiatrists that ME/CFS is a behavioural disorder that can be ameliorated by cognitive restructuring and incremental aerobic exercise (this invalidated view being the basis of the £5 million MRC PACE Trial and the £8.5 million national "CFS" clinics). This £13.5 million could and should have been much better spent on soundly-based research studies that were submitted to the MRC for grant funding (but which were rejected by the psychiatrists) or on a centre of excellence for translational medicine that addresses the biomedical abnormalities and the medical needs of ME/CFS patients.

Indeed, incremental aerobic exercise is contra-indicated in ME/CFS: non-state-sponsored UK research funded by the charity ME Research UK (MERUK) that was carried out by researchers under Professor Jill Belch, Professor of Vascular Medicine at Dundee (Head of the Vascular and Inflammatory Diseases Research Unit at Ninewells Hospital) has demonstrated an abnormal level of an inflammatory chemical in the blood that is matched by abnormal white blood cell behaviour (apoptosis) not only in adults but also in children with ME/CFS and the data are consistent with a reactivating or persistent viral infection (Arch Paediatr Adolesc Med 2010:164(9):817-823). The importance of this study cannot be over-emphasised because of the potential long-term consequences for cardiovascular disease and because the white blood cells are releasing an excessive amount of highly reactive free radicals, levels of which are even further increased by exercising muscle.

7. Far from being a behavioural disorder as deemed by the MRC PACE Trial Investigators, the top ten biomedical research findings in ME/CFS were summarised in 2008 by Anthony Komaroff, Professor of Medicine at Harvard and author of more than 230 research papers on ME/CFS; they include evidence that:

(1) many patients with ME/CFS have no diagnosable psychiatric disorder and ME/CFS is not a form of depression

(2) there is a state of chronic, low-grade immune activation, with evidence of activated T cells and evidence of genes reflecting immune activation, as well as evidence of increased levels of cytokines

(3) there is substantial evidence of poorly-functioning NK cells (white blood cells that are important in fighting viral infections)

(4) there are white and grey matter abnormalities in the brain

(5) there are abnormalities in brain metabolism (and evidence of dysfunction of energy metabolism in the mitochondria)

(6) there are abnormalities in the neuroendocrine system, particularly in the HPA axis but also in the hypothalamic-prolactin axis and in the hypothalamic-growth hormone axis

(7) there are cognitive difficulties, especially with information processing, memory and/or attention

(8) there are abnormalities in the autonomic nervous system (including a failure to maintain blood pressure, abnormal responses of the heart rate, and unusual pooling of blood in the legs, as well as low levels of blood volume)

(9) there is disordered gene expression, especially in those genes that are important in energy metabolism and in genes connected to HPA axis activity, to the sympathetic nervous system and to the immune system

(10) there is frequent infection with viruses, especially herpesvirus and enteroviruses.

Unlike the psychiatrists involved with the PACE Trial (who reject most of this evidence in favour of their own unproven beliefs), Professor Hooper, in common with international leading researchers and clinicians, is firmly convinced by it.

8. If the results of the PACE Trial are published and – given that the Principal Investigators actively sought and included those who do not suffer from ME/CFS in the trial cohort -- if the results are portrayed as positive evidence that behavioural interventions are successful for ME/CFS patients, such a travesty of scientific exactitude would surely bring dishonour and international ridicule on the MRC for approving the use of entry criteria that describe an unrelated disorder and for condoning a structured programme of belief modification expressly designed to change ME/CFS sufferers' correct cognitions that they suffer from a complex and chronic neuroendocrineimmune disorder that are supported by over 4,000 independent research studies.

Not only would this be likely to unleash international opprobrium on the MRC, it would also raise the issue of UK clinicians prescribing and using scientifically invalid, inappropriate and potentially dangerous interventions for seriously physically ill patients. This in turn raises the issue of patients' legal right of redress and the matter of GPs' professional responsibility to provide appropriate interventions that are based on medical science, not politics.

The Minister may recall that doctors were warned by the medical defence unions over ten years ago of possible legal consequences of prescribing exercise interventions that might lead to claims against them for inappropriate interventions, and that any form of exercise intervention must be prescribed with just as much caution as pharmacological interventions, otherwise they could be taken to court (ME Association Medical & Welfare Bulletin, Spring 2001, page 8).

Indeed, such was the concern about liability issues arising from inappropriate exercise interventions that in March 2000, the Department of Health sought advice from the Medical Protection Society. That advice (dated 29th March 2000) stated:

"*It is important that GPs do not feel that they are being asked to take on responsibilities for which they are not equipped. It would be helpful for there to be either national or local guidelines which set out specific conditions for which referral for a structured exercise programme is appropriate.*

"The introduction of the exercise professional who will be registered with a national body and have indemnity in respect of his work is welcomed…it will then be for the exercise professional to assess the suitability of the patient for a planned exercise programme of exercise, the content of which would be his responsibility".

The following year, 2001, the NHS published its "Exercise Referral Systems: A National Quality Framework Assurance", and on 8th March 2005 the Medical Advisor to the ME Association commented on it as follows:

"With increasing numbers of patients being prescribed exercise programmes on the NHS, doctors in the UK have once again been issued with guidance by one of their defence organisations and the Department of Health.

"This guidance is particularly important in view of the fact that people with ME/CFS are now being coerced into undertaking various types of graded exercise programmes – sometimes in a form that is totally inappropriate to their clinical situation.

"Doctors without specialist knowledge of exercise medicine – which will inevitably include most GPs and psychiatrists – should only 'recommend' exercise rather than 'prescribing' it. This is because referral and prescribing processes carry a greater legal implication and they have very specific meanings in the medical context. For example, if a doctor 'prescribes' exercise for a patient who then suffers a heart attack while exercising, the doctor could then face a claim for damages. So exercise programmes have to be 'prescribed' with just as much caution as is applied to the use of drugs.

"The DoH have also announced that they will be offering three year training courses in exercise medicine to doctors in an attempt to try and avoid some of the medico-legal dilemmas that are clearly associated with this approach to management".

This appears to mean that by "recommending" incremental graded exercise for people with ME/CFS in its Clinical Guideline 53 on "CFS/ME", NICE has placed legal responsibility for "prescribing" graded exercise onto GPs, consultants and psychiatrists – and also onto the Occupational Therapists who run the "CFS" clinics – when the majority of them are not, as required by the Department of Health, on the Register of Exercise Professionals (REP), sometimes known as the Exercise Register, and who thus do not comply with the Department of Health's own guidance about exercise interventions on the NHS. It is notable that the NICE Guideline contains no mention of this.

The implications for the MRC PACE Trial appear to be similar, in that the exercise therapists employed in the trial may also be in breach of the Department of Health guidance, because "*qualification as a physiotherapist does not automatically imply eligibility for the register*" (http://www.exerciseregister.org/documents/JoinPhysios2010.pdf). There is, however, an additional consideration: the "prescribing" of exercise interventions does not apply within a clinical trial where participants have given consent (ie. because the participants themselves have made the decision to try incremental graded exercise). However, it is part of Professor Hooper's complaint that PACE Trial participants were unable to provide fully informed consent because the information they received did not disclose (alternatively did not make clear) that the programme of incremental

graded exercise was predicated on the assumption that there is no organic pathology in ME/CFS and that participants were merely deconditioned (Graded Exercise Therapists' Manual, page 22).

As many researchers have shown, and as the Medical Advisor to the ME Association has pointed out, ME/CFS patients do not respond to exercise in the same way as other people (Shepherd C; Physiotherapy 2001:Aug; 87(8):395-396). The 2003 Canadian Consensus Definition and Guidelines on ME/CFS (rejected by Wessely School psychiatrists and by those agencies of state to which they act as advisors, including the Department for Work and Pensions, the MRC and NICE) are unambiguous: "*Exercise programmes must be entered cautiously as clinical studies have indicated that symptoms are worsened in approximately half of the ME/CFS patients….We must be very careful concerning any programme that presupposes that patients are merely wrongheaded about their illness and activity limits".*

The extensive scientific evidence showing that incremental aerobic exercise may be contra-indicated in ME/CFS, together with abundant evidence from numerous surveys by UK ME/CFS charities of almost 5,000 patients that exercise is unacceptable and is positively harmful in 50% of cases appears to make no impression on those who support the MRC PACE Trial, which is a matter of international on-going concern.

Professor Hooper thinks that the Minister will also recall that in March 2003 the House of Commons Science and Technology Select Committee produced its report "The Work of The Medical Research Council" (Third Report of Session 2002-03: HC 132) in which MPs issued a damning judgment on the MRC, lambasting it for wasting funds and for introducing misguided strategies for its research. MPs found evidence of poor planning and of focusing on "*politically-driven*" projects that have diverted money away from top-quality proposals. The unprecedented and excoriating attack was the result of a detailed probe into the workings of the MRC.

On 25th March 2003 The Times carried an article by Mark Henderson entitled "Research funding wasted on useless projects, say MPs". The article noted that the MRC had four Boards to advise on priorities in particular fields. It said the MRC: *"is refusing far too many high-quality grant applications …in favour of high-profile projects that had not been thought through. Financial mismanagement meant that studies of second-rank quality had been supported, only for more important research to be rejected".*

On the same day The Guardian carried a similar article by Donald MacLeod ("Medical Council accused of bad management"). That article said: "*The Committee found evidence of poor financial management and poor planning, leading to large numbers of top quality grant proposals being turned down".* The article quoted from the House of Commons Report: " *'Our impression is that a*

case has been put together by the funders to support a politically driven project' ". That the PACE Trial is a prime example of a politically-driven project can no longer be in doubt.

Similar articles appeared in The Edinburgh News (*"The House of Commons Science and Technology Committee today reported 'areas of serious concern' about the way the MRC distributes its grants. Committee Chairman Dr Ian Gibson said: 'Something has gone badly wrong at the MRC' ")* and The Scientist *("Perhaps the most disturbing accusation is that some of the best medical scientists in the UK have been starved of cash because of the MRC's preference").*

The ME/CFS community was aware that one of the main proponents of the behavioural model, psychiatrist Professor Simon Wessely, was a member of three Boards at the MRC: the Monitoring and Evaluating Steering Group which conducts evaluations of the MRC's research funding policies; the Neurosciences and Mental Health Board and the Health Services and Public Health Research Board.

During the MRC's Public Consultation period in 2002-2003 on the future of ME/CFS research in the UK, yet more members of the Wessely School were appointed to MRC Boards, including Trudie Chalder (a mental nurse who became a behaviour therapist, now Professor of Cognitive Behavioural Psychotherapy at the Institute of Psychiatry and one of the PACE Trial Principal Investigators), Anthony Cleare (Senior Lecturer in Affective Disorders and Director of the National Affective Disorders Unit at the Institute of Psychiatry, who claims to specialise in ME/CFS), Anthony David (Professor of Cognitive Neuropsychiatry at the Institute of Psychiatry and Consultant Psychiatrist), Anne Farmer (Professor of Psychiatric Nosology at the Institute of Psychiatry), Michael Sharpe (who now holds a Personal Chair in Psychological Medicine and Symptoms Research at Edinburgh and who is one of the PACE Trial Principal Investigators), Til Wykes (Professor of Clinical Psychology at the Institute of Psychiatry) and Peter White (Professor of Psychological Medicine, Barts and Queen Mary's School of Medicine, the PACE Trial Chief Principal Investigator).

It is notable that in 2005 (ie. during the life of the PACE Trial), a 32 page Report from a Working Group of the Medical Research Council's Neurosciences and Mental Health Board (NMHB) Strategy and Portfolio Overview Group (SPOG) was clear that, despite the formal WHO classification of ME/CFS as a neurological disorder, the MRC considers ME/CFS to be a mental disorder and will continue to do so: at paragraph 6.2 the Report is unequivocal: *"Mental health research in this instance covers CFS/ME".* This is an explicit denial of the repeated Government statements that it accepts and endorses the WHO classification of ME/CFS as a neurological disorder.

As Dr Jonathan Kerr, formerly of the Department of Cellular and Molecular Medicine at St George's University of London (whose grant application for gene research in ME/CFS was rejected by the

MRC) said on the record at the Invest in ME International Conference in May 2007 held in London, as long as psychiatrists control the MRC, it will never fund biomedical research into ME/CFS.

It is time that the MRC is held publicly to account over its misplaced support for the out-dated and indefensible behavioural model that lacks scientific rigour and credibility and is so damaging to people whose lives are wrecked by ME/CFS. As responsibility for the MRC falls within the Minister's remit, it is his duty to ensure that this situation is not allowed to continue.

Professor Hooper once again asks that you inform both BIS officials and the MRC itself of the contents of this letter, for which I should be grateful if you would acknowledge receipt.

Kind regards

Margaret Williams