Sent on behalf of Malcolm Hooper, Emeritus Professor of Medicinal Chemistry
2, Nursery Close, Sunderland, SR3 1PA

Matthew Wicks
Private Secretary to the Rt Hon David Willetts MP
Minister of State for the Department of Business, Innovation and Skills
1, Victoria Street
LONDON SW1H 0ET

19th January 2011

Dear Matthew,

Professor Hooper notes that as yet, he has received no response to his last two communications to the Minister concerning his 11-month old complaint about the MRC PACE Trial and, despite the Minister's promise in his letter of 8th November 2010, he has received no response at all from the MRC.

Notwithstanding, he is sure that the Minister and the officials at BIS who are dealing with the MRC about his complaint would wish to be informed that a recent study in Spain has found that in (ME)CFS patients, the two interventions used in the MRC PACE Trial, CBT and GET, including pharmacological interventions, 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; Clin Rheumatol 2011, Jan 15: Epub ahead of print).

The Minister will already be aware of the widespread concern about the PACE Trial amongst international healthcare professionals who specialise in ME/CFS (see, for example: "Statements of Concern about Cognitive Behavioural Therapy and Graded Exercise Therapy provided for the High Court Judicial Review of February 2009", extracts of which are available athttp://www.meactionuk.org.uk/JR_Statements_-_extracts.htm). Such concern is mounting.

The Minister will doubtless recall from previous correspondence that the MRC PACE Trial entry criteria (the Oxford criteria: Sharpe et al. JRSM 1991:84:118-121) do not require the presence of the hall-mark symptom of ME/CFS (ie. post-exertional fatigability with malaise), causing the scientific community consternation about exactly what disorder is being investigated at a cost of over £5 million.

It cannot by definition be ME/CFS as the Investigators allege, since the pathognomonic feature of ME/CFS is not required to be present in PACE Trial participants. The Trial protocol gives no indication of measuring, investigating or even acknowledging the cardinal symptom, yet this might be the very symptom that would provide reliable information about patients who would be expected not to improve on the PACE Trial interventions and for whom incremental aerobic exercise would be contra-indicated.

There is an abundance of research confirming this widely reported phenomenon. For ease of reference, the following sources (some of which pre-date the PACE Trial) discuss the cardinal symptom of ME/CFS that the Trial Investigators continue to ignore:

1999: Paul et al investigated delayed recovery from fatiguing exercise in chronic fatigue syndrome and confirmed*: "Recovery was prolonged in the patient group, however, with a significant difference compared to initial MVCs being evident during the recovery phase after exercise (P = 0.001) and also at 24 h (P < 0.001). In contrast, the control group achieved MVCs which were not significantly different from initial values during the recovery phase, and maintained these at 24 h.* ***These findings support the clinical complaint of delayed recovery after exercise in patients with CFS****"* (Journal of European Neurology 1999:6(1):63-69)

2002: The Chief Medical Officer's Working Group Report states*: "Perhaps the prime indicator of the condition is the way in which symptoms behave after activity is increased beyond what the patient can tolerate.* ***Such activity, whether physical or mental, has a characteristically delayed impact, which may be felt later the same day, the next day, or even later. This is followed by a recovery period, which again may last for days or even weeks"*** (Report of the CFS/ME Working Group, January 2002)

2005: Jammes et al explored "Chronic fatigue syndrome: assessment of increased oxidative stress and altered muscle excitability in response to incremental exercise". The research concluded*:* ***"The response of CFS patients to incremental exercise associates a lengthened and accentuated oxidative stress together with marked alterations of the muscle membrane excitability. These two objective signs of muscle dysfunction are sufficient to explain muscle pain and postexertional malaise reported by our patients"*** (Journal of Internal Medicine 2005:257(3):299-310)

2007: The NICE Guidelines for CFS/ME state: *"1.2.1.2 Healthcare professionals should consider the possibility of CFS/ME if a person has: fatigue with all of the following features:…****characterised by***

post-exertional malaise and/or fatigue (typically delayed, for example by at least 24 hours, with slow recovery over several days)" (NICE Full Clinical Guideline 53, August 2007)

2007: The Department of Work and Pensions Specialist Guide (DWP 2007) says about patients with CFS: *"Often they feel symptoms more after physical or mental activity, even minor exertion within the home environment, and* ***this effect is characteristically delayed until the next day or so, and is prolonged"*** (DWP Specialist Guide CFS/ME, 2007)

2008: Sorensen et al investigated "Transcriptional control of complement activation in an exercise model of chronic fatigue syndrome" and summarised their research*: "Virtually all those who suffer from CFS note that their symptoms are made much worse following exercise and postexertional malaise may be a unique and major CFS defining symptom...* ***We found that genes contributing to one of these pathways responded to exercise challenge differently in persons with CFS compared to well controls and hypothesize that this may account for increased inflammation-mediated postexertional malaise in people with CFS"*** (Molecular Medicine 2008:15:34-42)

2008*:* In their paper "Diminished Cardiopulmonary Capacity During Post-Exertional Malaise", VanNess et al state: *"Reduced functional capacity and post-exertional malaise following physical activity are hallmark symptoms of Chronic Fatigue Syndrome (CFS). That these symptoms are often delayed may explain the equivocal results for clinical cardiopulmonary exercise testing with CFS patients",* concluding: "*In the absence of a second exercise test, the lack of any significant differences for the first test would appear to suggest no functional impairment in CFS patients. However, the* ***results from the second test indicate the presence of a CFS related post-exertional malaise"*** (JCFS 2008:14(2):77-85)

2010: In their paper "Unravelling the nature of postexertional malaise in myalgic encephalomyelitis / chronic fatigue syndrome: the role of elastase, complement C4a and interleukin-1ß" Nijs et al stated: *"Too vigorous exercise or activity increase frequently triggers postexertional malaise in people with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), a primary characteristic evident in up to 95% of people with ME/CFS…* ***Postexercise complement C4a level was identified as a clinically important biomarker for postexertional malaise in people with ME/CFS"*** (Journal of Internal Medicine 2010:267:418-435)

2010: VanNess et al investigated "Postexertional malaise in women with chronic fatigue syndrome" and concluded: ***"The results of this study suggest that PEM is both a real and an incapacitating condition for women with CFS and that their responses to exercise are distinctively different from those of sedentary controls"*** (Journal of Womens Health 2010:19(2):239-244)

2011: When Davenport et al investigated the "Diagnostic accuracy of symptoms characterising chronic fatigue syndrome", they found that *"fatigue demonstrated high sensitivity and modest specificity to distinguish between cohorts".* This 'modest specificity' related to distinguishing CFS from sedentary controls. For distinguishing CFS from other fatigue conditions such as chronic IM, anxiety or depression, burnout etc, 'fatigue' is likely to be unspecific. However, Davenport et al found that *"failure to recover within 1 day"* proved to be sensitive and specific*: "**Clinimetric properties of failure to recover within 1 day to predict membership in the CFS cohort were sensitivity 0.80, specificity 0.93**…"* (Disability and Rehabilitation, 6th January 2011: Epub ahead of print).

You will no doubt recall the letter of 12th January 2011 sent to you by a correspondent (CB) from Surbiton, Surrey, which was sent as a result of our last letter to you of 5th January 2011. This woman (previously unknown to us) spent her professional life working in welfare benefits and social care and now suffers from severe ME and, following two unsuccessful Appeals about DLA, is in danger of losing her home. Her letter sets out her personal experience of CBT and GET, which was that they caused her condition to worsen. Her letter (entirely unsolicited by us) reflects our own concerns about the MRC PACE Trial. For example, she points out:

*"Sutton Hospital's Chronic Fatigue Clinic is supportive of GET, and CBT underpins their CFS 'Lifestyle Management' course which I attended….I am totally convinced that this is **not**appropriate treatment of ME. In many cases, continued emphasis on challenging patterns of behaviour is counter-productive in that it deflects from dealing with the real problems faced by people with ME"*

"…there is a very serious side to the perception that people with ME don't have a 'real' illness or are 'mental' or feckless. This view is widespread among the people who are tasked with supporting people with ME, for example, welfare benefits Decision Makers (Employment & Support Allowance, Disability Living Allowance, Housing Benefit etc), the Atos doctors who advise them, public and private sector ill-health pension Decision Makers, personal care-givers, domestic helpers, health and social care professionals etc. The effect of this is that ill-health benefits and pensions are incorrectly denied, access to personal and/or domestic assistance is restricted, and every relationship is underpinned by this negative view of ME….If it were only the general public that thought like this, it would just be regrettable, but unfortunately our politicians and even many medical professionals hold this view too"

"The PACE trial was, it seems, set up with a preconceived belief that ME/CFS is part psychological and part deconditioning. This view is out-dated, disparaging and just plain wrong"

"The government must ensure that future trials are wholly impartial and that this damaging, mistaken view is eradicated"

"I have copied this letter to…the Secretaries of State for Health and for Work & Pensions, and my MP, because my comments may help…to emphasise just how important their actions and views are on this issue in their spheres of influence".

The Minister will be aware from our previous correspondence that the insurance industry cites the NICE Guideline CG53 in support of its refusal to pay out for ME/CFS claims; it interprets the Guideline's lack of acceptance of ME/CFS as a neurological disorder as evidence that it is a somatoform disorder and, quite certainly, the MRC PACE Trial is predicated on the same assumptions.

The harrowing personal consequences of these insupportable assumptions are described by CB in her letter to you of 12th January 2011.

The matter of Professor Hooper's complaint about the MRC PACE Trial is gaining international momentum on the internet and he again asks that his concerns are addressed with due diligence and that the Minister ensures they are expedited.

Kind regards

Margaret Williams