Professor Hooper's Initial Response to the MRC PACE Trial Press Release hosted by The Lancet

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1. The MRC PACE Trial used the Oxford criteria which do not define patients with ME/CFS. If used correctly, they exclude people with neurological disorders yet ME is a classified neurological disorder (WHO ICD-10 G93.3). The Trial's *"operationalised Oxford research diagnostic criteria for CFS"* (Trial Protocol version 5, 2006, Section 7.2) were partly financed by the Chief Principal Investigator's (Professor Peter White) own money (JRSM 1991:84:118-121). Professor White's American peers have pointed out that the UK estimates (that are based on the Oxford criteria) are likely to include a high percentage of patients with psychiatric morbidity (*"It is at least possible that the 2.54% to 2.6% rates in both the United States and Great Britain are due to a broadening of the case definition and possible inclusion of cases with primary psychiatric conditions. Some CFS investigators would not see this as a confounding problem because they believe that high rates of psychiatric comorbidity indicate that CFS is mainly a psychiatric disorder….Most importantly, the erroneous inclusion of people with primary psychiatric conditions in CFS samples will have detrimental consequences for both the interpretation of both epidemiological and treatment efficacy findings"* (Professor Leonard Jason: Problems with the New CDC CFS Prevalence Estimates: IACFS/ME: 2007; Professor Leonard Jason: How Science can stigmatise: the case of Chronic Fatigue Syndrome. JCFS 2007:14:85-103). A Canadian psychiatrist who specialises in ME/CFS, Dr Ellie Stein, said on 25th May 2007 at the ME Research UK International Research Conference held at the Edinburgh Conference Centre, Heriot Watt University, that the Oxford criteria "*could describe almost anybody. I do not believe that studies which use the Oxford criteria can be generalised to patients which most of us in this room would consider to have ME/CFS*". Indeed, on 14th July 2006 Professor White sought Ethics Committee approval to advertise his PACE Trial to GPs, asking them to refer anyone *"whose main complaint is fatigue (or a synonym)".* The MRC PACE Trial entry criteria had an "open door" policy and did not identify people with ME/CFS (those supposedly under study in the PACE Trial), hence the reported results cannot be claimed to refer to ME/CFS patients.

2. The MRC PACE Trial excluded children and those who are severely affected. The results of any trial that excluded those who are severely affected cannot be taken seriously.

3. The MRC PACE Trial used no objective measures of outcome (ie. actigraphy) to show improvement or non-improvement and relies upon participants' subjective answers to questionnaires. This is an unscientific way to gather evidence. There can be no empirical science without objective measures – objective measures are at the heart of the scientific method.

4. Professor White has claimed that CBT and GET can cure people with ME/CFS, for example, **he claims that *"a full recovery is possible"*** (Psychother Psychosom 2007:76(3):171-176) and **the participants' CBT Manual informs people that the PACE Trial therapies are curative** and that "*many people have successfully overcome their CFS/ME"* with such behavioural interventions ("Information for relatives, partners and friends", page 123). Moreover, in the NHS Plus Report, for which Peter White was an external assessor but failed to reveal that he was peer-reviewing his own work (Occupational Aspects of the Management of Chronic Fatigue Syndrome, October 2006), it was claimed that CBT/GET have been shown to be effective in restoring the ability to work in those who were absent from work. However, in a Statement in 2009 for the British High Court, his American peers doubted the possibility of the 23% to 25% recovery rate that Peter White claimed he had achieved (http://www.meactionuk.org.uk/JR_Statements_-_extracts.htm). Commenting on her own recently co-authored paper on CBT (C. Lopez et al, Journal of Psychosomatic Research 2011: doi: 10.1016/j.jpsychores.2010.11.010 Epub ahead of print), Professor Nancy Klimas said on the record: "*Dr White challenged me in a meeting a year ago saying nothing else had been published to deny this finding. So now you have a publication, written by a psychologist and well-regarded CBT expert to use when you want to argue that CBT helps people with this illness (as it does in every chronic disease model ever tested) but does not cure the illness"* (http://networkedblogs.com/dG7pU).

5. The recent drugs industry scandal concerning Avandia has resonance for ME/CFS research. The editor of the BMJ, Fiona Godlee, concluded that pharmaceutical companies could not be trusted to generate honest research in respect of their own products and that independent scientific corroboration would always be required. The same principle should apply to non-pharmaceutical research, but the only research supporting CBT/GET has been generated by those who stand to gain most in professional and financial terms from its promotion. Similar independent corroboration should be required before experimental psychological interventions are applied nationally.

6. Professor White and his co-Principal Investigators all have financial links with the health insurance industry, a matter of grave concern to the former Chairman of a House of Commons Science and Technology Select Committee and former Dean of Biology (Dr Ian Gibson MP); a member of the Home Affairs Select Committee (Ann Cryer MP); a Minister of State for the Environment (The Rt Hon Michael Meacher MP); a former President of the Royal College of Physicians (Lord Turnberg); the Deputy Speaker of the House of Lords (the Countess of Mar), and a former Health Minister and Honorary Fellow of the Royal College of Physicians (Baroness Julia Cumberledge) (Gibson Inquiry Parliamentarians' Report, 2006). In an obvious reference to Professor White, this Report stated: "*There have been numerous cases where advisors to the DWP have also had consultancy roles in medical insurance companies, particularly the company UNUMProvident. Given the vested interest that private medical insurance companies have in ensuring CFS/ME remains classified as a psychosocial illness, there is a blatant conflictof interest here. The Group finds this to be an area for serious*

concern…". In Professor White's case, this blatant conflict of interest remains unresolved, as he is Chief Medical Officer for the insurance giant Swiss Re, and another of the PACE Trial Principal Investigators, Professor Michael Sharpe, is associated with UNUMProvident.

7. There is existing acknowledgement that there is no long-term benefit from CBT:

   - Professor Simon Wessely, who directed the PACE Clinical Trial Unit, is on record stating that CBT provides no effective treatment: in his Editorial (JAMA 19th September 2001:286:11) he stated that CBT and GET are only "*modestly effective*" and that neither is "*remotely curative*".

   - Wessely is also on record as stating: *"It should be kept in mind that evidence from randomised trials bears no guarantee for treatment success in routine practice. In fact, many CFS patients, in specialised treatment centres and the wider world, do not benefit from these interventions"* (The act of diagnosis: pros and cons of labelling chronic fatigue syndrome. Marcus JH Huibers and Simon Wessely. Psychological Medicine 2006:36: (7): 895-900).

   - It would surely have been better if the (more than) £5 million spent on investigating what was already known had been spent on biomedical research into this complex disorder and in helping the severely affected (for instance, by providing domestic and personal assistance) and on effective pain relief for those afflicted.

8. The Adaptive Pacing Therapy (APT) used in the PACE Trial is not the same as pacing, a common sense approach that patients find helpful. The CBT Therapists' Manual states about APT: "*Activity is therefore planned"*, which indicates a structured activity regime, and the APT Therapists' Manual lists other requirements for APT including "*plan set activity in advance"* (so activity must be *"set activity"*, not simply what the patient may be capable of doing at the time)*;* there must be *"activity analysis"*; APT participants must *"constantly review model, diaries and activity"* and there is the requirement to *"involve relatives"*, which is nothing like "doing what you can when you can". Professor White is on record as being strongly opposed to pacing: "***The theoretical risk of pacing is that the patient remains trapped by their symptoms in the envelope of ill-health"*** (Editorial: Postgrad Med J. 2002:78:445-446), so it was unlikely that he would find pacing to be effective. This should be contrasted with his American counterparts, who promote the "energy envelope" management strategy (The impact of energy modulation on physical function and fatigue severity among patients with ME/CFS. Leonard Jason et al; Patient Educ Couns 2009:77:237-241).

9. The MRC FINE Trial (sibling of the PACE Trial) failed spectacularly. It found that "pragmatic rehabilitation" (PR, based on CBT/GET) was minimally effective in reducing fatigue and improving sleep only whilst participants were engaged in the programme and that there was no statistically significant effect

at follow-up. Furthermore, pragmatic rehabilitation had no statistically significant effect on physical functioning; equally, its effect on depression had diminished at follow-up. Moreover the other intervention being tested ("supportive listening" or SL) had no effect in reducing fatigue, improving physical functioning, sleep or depression.

10. The results of the PACE Trial may mean that patients who have genuine ME as opposed to chronic "fatigue" will continue to be denied appropriate investigation and treatment; they may be deprived of State benefits necessary for survival; their insurance claims may be rejected, and they will be condemned to an even lower quality of life.

11. The results of the MRC PACE Trial were anticipated to be in favour of the interventions being studied because the Trial is but one prong of a UK Blair Government three-pronged "integrated plan" to roll out CBT and GET across the nation for those with ME/CFS (Department of Health, 2004, Statement of Information released via the Welsh Assembly Disclosure Log 2296), the other two prongs being the NICE Clinical Guideline 53 published in August 2007 and the national "Fatigue" Clinics that cost taxpayers £8.5 million to deliver an intervention known to be ineffective and to have made at least 50% of those who have undertaken it actively worse. The "integrated plan" was designed to ensure compliance, so it was never in doubt that the PACE Trial results would conform to the "integrated plan", as indeed is the case (ie. CBT and GET are said to be safe and moderately effective treatments for everyone with ME/CFS and to be better than APT).

12. On 12th October 1996, a Lancet editorial about the Joint Royal Colleges' Report on CFS noted that psychiatrists had monopolised the research and management of ME/CFS: "*The sixteen strong committee was top heavy with psychiatric experts, so the emphasis on psychological causes and management is no surprise. Charles Shepherd, Medical Director for the ME Association, told us: 'The committee was rigged, with dissenting voices excluded'."* Unfortunately, nothing has changed in the fifteen years since. Except apparently the Lancet editorial policy.

For a detailed analysis of the whole PACE Trial, including evidence of the in-built facility for the DWP to have unrestricted access to participants' medical notes; the fact that participants' data was not kept securely and was stolen but they were not informed of this; the apparent failure of the Principal Investigators to adhere to the Declaration of Helsinki; the fact that some participants were told --- against the basic rules of any clinical trial --- that the intervention they were receiving was curative; the dilution of the entry criteria after the trial had commenced (so the second and subsequent tranches of participants were less ill and thus more likely to respond favourably to the interventions); the apparent lack of clinical equipoise, and the fact that the Trial manuals describe behaviours and techniques to be used by the Trial therapists that should not --- and cannot --- be considered ethical by an independent and reasonable observer, see "Magical Medicine: how to make a disease disappear": http://www.meactionuk.org.uk/magical-medicine.htm .

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