

Initial response by Professor Malcolm Hooper to an undated letter sent by Professor Peter White to Dr Richard Horton, Editor-in-Chief of The Lancet

18th May 2011

On 17th May 2011 Zoe Mullan, Senior Editor at The Lancet, sent an email to Professor Hooper in response to the complaint he submitted about the PACE Trial article published online by The Lancet on 18th February 2011 and subsequently in the journal on 5th March 2011. In her email, Zoe Mullan wrote: *"We asked the authors of the PACE trial to respond to your concerns, which they have duly done. Your complaint and their response were discussed at the highest management level and this group of executive editors was fully satisfied that there were no grounds whatsoever on which to take further action. We attach the response provided to us here. From an editorial perspective, the case is now closed"*.

The undated response to Professor Hooper's complaint by Professors White, Sharpe and Chalder that was sent to Dr Richard Horton (Editor-in-Chief of The Lancet) on behalf of all the co-authors will, in the interests of openness and transparency, be placed in the public domain and will be fully addressed in due course, as will Professor Hooper's concerns over what he believes is the failure of The Lancet's editorial process in this instance, but there is one point in Professor White's letter that is of particular importance, so it is addressed in this initial response.

In their letter, Peter White et al state: ***"The PACE trial paper refers to chronic fatigue syndrome (CFS) which is operationally defined; it does not purport to be studying CFS/ME"***.

The sentence continues by stating that the PACE Trial studied: ***"CFS defined simply as a principal complaint of fatigue that is disabling, having lasted six months, with no alternative medical explanation (Oxford criteria)"***.

This is exactly what the ME/CFS community has been saying from the outset, namely that the PACE Trial was not studying those with ME.

Soon after the Oxford criteria were published in 1991, one of the co-authors, psychiatrist Anthony David, wrote in the British Medical Bulletin: ***"British investigators have put forward an alternative, less strict, operational definition which is essentially chronic...fatigue in the absence of neurological signs, (with) psychiatric symptoms...as common associated features"*** (AS David; BMB 1991;47:4:966-988).

Given that ME is a classified neurological disorder (ICD-10 G93.3), there thus ought to have been no dispute that the PACE Trial Investigators were not studying those with ME, but the Investigators have persistently confirmed that they were studying those with ME, for example:

1. The PACE Trial Identifier is clear: ***"Myalgic encephalomyelitis is thought by most to be synonymous with CFS"*** (PACE Trial Identifier; 2.1). The cited references for this statement are given as (i) Fukuda K et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med 1994; 121: 953-959; (ii) Sharpe MC et al. A report – chronic fatigue syndrome. JR Soc Med 1991; 84: 118-121; (iii) Wessely SC et al. Chronic fatigue and its syndromes. Oxford, Oxford University Press, 1998; (iv) Working group report to the Chief Medical Officer, www.doh.gov.uk/cmof/cfsmereport 2002 and (v) NHS Centre for Reviews and Dissemination. Interventions for the management of CFS/ME. Effective Health Care 2002; 7(4): 1-12.
2. The two versions of the PACE Trial Protocol (both the Full Protocol and short version that was published in BMC Neurology 2007:7:6) are equally clear; the PACE Trial was: ***"A randomised controlled trial of adaptive pacing, cognitive behaviour therapy, and graded exercise as supplements to standardised specialist medical care versus standardised specialist medical***

care alone for patients with the chronic fatigue syndrome/myalgic encephalomyelitis or encephalopathy".

3. In the Glossary to the Full Protocol, Professor White et al specifically state that CFS/ME is **the official term** for the illness described in the **"Working Group Report to the Chief Medical Officer (2002) and the MRC RAG Report (2003)"**.
4. In the PACE Trial Patient Clinic Leaflet, Professor White et al state: **"This illness is also known as post-viral fatigue syndrome, myalgic encephalomyelitis (ME) and myalgic encephalopathy (ME). Medical authorities are not certain that CFS is exactly the same illness as ME...but we will be calling this illness CFS/ME"**.

In The Lancet article itself, Peter White et al use the term myalgic encephalomyelitis throughout the text and actually state: **"Myalgic encephalomyelitis is thought by some researchers to be the same disorder...Several diagnostic criteria exist for chronic fatigue syndrome and myalgic encephalomyelitis"**, thus implying that they had indeed studied those with ME.

Moreover, in the authors' reply published in the Lancet on 17th May 2011 (The PACE trial in chronic fatigue syndrome – Authors' reply), Peter White is unambiguous: **"...however we defined CFS and myalgic encephalomyelitis, we found that cognitive behaviour therapy and graded exercise therapy provided a significant and clinically useful advantage...."**

Here, though, Professors White, Sharpe and Chalder have categorically stated that the PACE Trial **"does not purport to be studying CFS/ME"**.

This may explain why so many recruits were not accepted into the PACE Trial on the stated grounds they did not fulfil the Oxford criteria for "CFS" (which according to the Principal Investigators themselves, is not the same as "CFS/ME").

If the PACE Trial was not studying CFS/ME (as now asserted by Professor White et al), then the results cannot be used by NICE to support its Clinical Guideline 53 for CFS/ME.

NICE, however, announced on 14th March 2011 that there will be no review of CG53 until 2013: **"...interventions recommended in the original guideline, such as CBT and GET, were described as the interventions for which there is the clearest evidence-base of benefit. This is supported by the recently published PACE trial...The results of the study are in line with current NICE guideline recommendations on the management of CFS/ME...There are no factors...which would invalidate or change the direction of the current guideline recommendations. The CFS/ME guideline should not be updated at this time"**.

Most certainly, this statement by the Principal Investigators that the PACE Trial did not purport to be studying those with CFS/ME raises important issues about the alleged generalisability of the PACE Trial results, given that The Lancet article unambiguously states: **"The PACE findings can be generalised to patients who also meet alternative diagnostic criteria for chronic fatigue syndrome and myalgic encephalomyelitis but only if fatigue is their main symptom"**.

That The Lancet supports the Principal Investigators' inconsistent and indefensible position and refuses to engage with clearly articulated complaints must be of concern to anyone interested in the integrity of the scientific process.