My complaint (originally by email dated 25 April 2011) to Richard Horton, editor of

The Lancet,

regarding their publication of the PACE trial

Angela Kennedy

Dear Doctor Horton,

Further to my email correspondence with one of your colleagues, Zoe Mullan, about the PACE trial, I am writing to you to complain, formally, about the article: **White PD, Goldsmith KA, Johnson AL, et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy,**

graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. Lancet 2011; 377: 823-836.

The PACE trial was subject to a large amount of concern and objection by advocates for those diagnosed with ME or CFS, from the beginning of the study in 2004 and throughout its course. I was one of those who outlined specific concerns at the beginning of the trial: and various concerns were also outlined in response to the publication of the protocol mid-trial. For evidence of this please see my own and others comments at:

http://www.biomedcentral.com/1471-2377/7/6/comments/comments

I am writing primarily as the mother and long-term advocate of a child (now a woman) diagnosed at 13 with ME/CFS, and who has various objective, medically substantiated organic impairments (especially neurological and cardiovascular) which have led to severe disability. If subjected to PACE-type CBT and GET, she would be at serious risk of further harm.

There remain a large number of very serious flaws, problems and discrepancies in this whole study, including the published article in the Lancet. I am writing to reiterate the many substantive and valid concerns raised by Professor Malcolm Hooper in his complaint to you about this article and the trial itself, available here:

http://www.meactionuk.org.uk/COMPLAINT-to-Lancet-re-PACE.htm

http://www.meactionuk.org.uk/COMPLAINT-to-Lancet-re-PACE.doc

I am also aware that a large number of valid and substantive criticisms of the trial have been made in letter form to the Lancet and have been rejected for publication.

In addition to the above concerns, I am specifically gravely concerned about the dangers to patients caused by the unsafe claims that Cognitive Behavioural Therapy of the type advocated by White et al, and Graded Exercise Therapy, are safe treatments for people diagnosed with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, claims propounded both within the PACE article itself, and the accompanying editorial. This has led to similar unsound claims being made elsewhere. The potential adverse ramifications for patients of these unsound claims are particularly serious, and therefore those claims should not have been made.

Bleijenberg and Knoop, in their Lancet editorial accompanying the publication of the PACE article, claim:

"*Concerns about the safety of cognitive behaviour therapy and graded exercise therapy have been raised more than once by patients' advocacy groups. Few patients receiving cognitive behaviour therapy or graded exercise therapy in the PACE trial had serious adverse reactions and no more than those receiving adaptive pacing therapy or standard medical care, which for cognitive behavioural therapy has already been shown…This finding is important and should be*

communicated to patients to dispel unnecessary concerns about the possible detrimental effects of cognitive behaviour therapy and graded exercise therapy, which will hopefully be a useful reminder of the potential positive effects of both interventions."

The PACE article itself states:

"*Trial findings show cognitive behaviour therapy (CBT) and graded exercise therapy (GET) can be effective treatments for chronic fatigue syndrome, but patients' organisations have reported that these treatments can be harmful and favour pacing and specialist health care. We aimed to assess effectiveness and safety of all four treatments*."

The same article concludes:

"*Findings from the PACE trial suggest that individually delivered CBT and GET, when added to SMC, are more effective and as safe as APT added to SMC or SMC alone. Patients attending secondary care with chronic fatigue syndrome should be offered individual CBT or GET, alongside SMC."*

Other parties have repeated these unsafe claims, informed by the PACE trial. One example of a newspaper article is that in the Daily Mail, on 18th February 2011, which claims:

"*Got ME? Fatigued patients who go out and exercise have best hope of recovery, finds study*".

A press release from the Science Media Centre about the trial included various unsound claims of safety from doctors. Alistair Miller, for example, stated:

"It provides convincing evidence that GET and CBT are safe and effective and should be widely available for our patients with CFS/ME".

Derick Wade, as another example, claimed that the trial:

"...confirms the effectiveness of two treatments, and their safety. The study suggests that everyone with the condition should be offered the treatment, and every patient who wishes to be helped should be willing to try one or both of the treatments".

In addition to the claim of safety of CBT and GET, Wade's comment also indicates that patients may be regarded as recalcitrant (for example, in a context of welfare support or continued medical support) should they, quite rationally, dare refuse to 'try' treatments that actually may be dangerous.

The fundamental problem that needs to be addressed is that the evidence available shows that, contrary to the above claims, the PACE trial did *not* adequately assess, or even address, safety of CBT and GET, and this study did *not* disprove patients and doctors' valid and substantive concerns regarding the dangers of CBT and GET. One major discrepancy of the PACE trial and the resulting article was the failure to address the biomedical evidence available detailing serious organic physiological dysfunction in patients who receive a 'CFS' or 'ME' diagnosis. Another is the inadequate treatment of adverse outcomes within the trial. This is discussed in more detail in Professor Hooper's document as detailed above.

I wish to raise specific concerns about the patient cohort. Evidence indicates that research cohorts for 'CFS' or 'CFS/ME' appear to be obtained (by those promoting psychogenic explanations for these conditions) by *excluding* patients with signs and symptoms (especially neurological) found in Myalgic Encephalomyelitis case descriptions, or indeed other organic diseases (the 'alternative diagnoses'). The PACE trial used, not just one case criteria to exclude

patients with symptoms and signs of organic disease from the trial, but three: 'Oxford' (Sharpe et al, 1991); Reeves et al (2003), and those from the NICE guidelines (see White et al, 2011: 2).

Of 3158 patients who had been referred to "six specialist chronic fatigue syndrome clinics in the UK National Health Service" (White et al, 2011: 2), 1187 patients (over a third) were actually *excluded* because they did not actually meet Oxford criteria for 'CFS'. Confusingly, no figures are given for those meeting Reeves et al (2003) and NICE exclusionary criteria, though these are

claimed as part of the exclusion process. This is possibly because the Oxford criteria themselves efficiently exclude those with signs and symptoms of neurological myalgic encephalomyelitis, to the point that the Reeves and NICE exclusionary criteria may well have been superfluous.

There are similarities of symptoms and signs of neurological dysfunction found in specific case descriptions of myalgic encephalomyelitis (for example, Ramsay, 1988), or 'ME/CFS' (as defined by Carruthers et al, 2003), with other neurological conditions, for just one example, those found in Multiple Sclerosis (see, for example, Poser 2000). Therefore, to have *included* patients with neurological symptoms and/or signs might have meant there was a risk of other neurological conditions (such as Multiple Sclerosis) being involved in the trial. Indeed, in his response to me on the biomedcentral site, Peter White discusses the need to keep people with other neurological conditions out of the trial. But, crucially, the key problem here is that, from the evidence available (some of which is detailed by Professor Hooper), Professor White and his colleagues do not appear to believe 'ME' is a neurological condition in the first place, despite the acceptance of this by the World Health Organisation and British agencies, and despite the evidence available to support this, and therefore seem unable to acknowledge that at least some people given an ME or CFS diagnosis have organic neurological and other deficits. It seems therefore likely that ME/CFS patients with signs and symptoms of neurological (and indeed other organic) dysfunction were actively *excluded* from the PACE trial.

Ironically, if this premise is accurate, White et al cannot have substantiated their claims for the safety and efficacy of CBT/GET for patients they claim such treatments are safe and efficacious, those given an ME or CFS diagnosis who suffer physiological impairments including neurological deficits. It needs to be noted that the PACE article actually claims the results:

"*can be generalised to patients who meet alternative diagnostic criteria for chronic fatigue syndrome and myalgic encephalomyelitis but only if fatigue is their main symptom*" (citing the London criteria and Reeves et al 2003 as the 'alternative diagnostic criteria').

This is a confusing statement, bearing in mind that: the 'London Criteria' used in PACE were not actually that as referenced by them (as the documentation from the PACE trial protocol shows); the Reeves et al criteria were supposed to have been used by them within the trial itself (so the question arises, why are they 'alternative'?); and their conclusions, and that of Bleijenberg and Knoop and others, presents a blanket claim of safety and efficacy for all people given a diagnosis of ME or CFS, contradicting this statement about "only if fatigue is their main symptom".

Indeed, it is notable that White et al, from the beginning of the trial and throughout, refused to use the criteria of Carruthers et al (2003) to include people with symptoms (and possibly signs) of neurological dysfunction, although they used their own (specifically customised and therefore different) version of a set of criteria claimed to identify ME (the 'London' criteria), already controversial due to lack of peer reviewed publication, uncertainty in authorship, and the existence of different versions. Indeed, as is evident from the PACE Trial protocol, the specifically customized PACE version of the 'London' criteria for ME bore close similarities to the Oxford criteria for CFS, and were fundamentally different to the Carruthers et al criteria (2003).

That so many patients (nearly a third), of whom had been referred to a 'specialist chronic fatigue syndrome unit' by their GP, were actually excluded from the CFS diagnosis favoured by these authors, is extremely important, and leads to the question: what happens to such patients? When the patient exclusion process of another project (the negative XMRV study by Erlwein et al, 2009) was clarified by co-authors (Wessely et al, 2010), some clinical patients who had attended chronic fatigue/CFS clinics commented in response that they had not been investigated thoroughly in the way the research cohorts appeared to be (ironically in order to exclude organic disease), either at the clinic or by their GP. Another study by Newton et al (2010) found that 40% of patients referred to a 'chronic fatigue syndrome unit' did not have 'CFS', though, crucially, Newton was including, as 'CFS' patients, those with specific physiological conditions such as positional orthostatic tachycardia syndrome (POTS), which are associated with neurological dysfunction (Carruthers et

al, 2003). If these patients had been also excluded from a diagnosis of CFS (which, according to the Oxford criteria and indeed the Reeves et al criteria, they should), the amount of patients referred to British ‘chronic fatigue syndrome units’ (or, often, ‘chronic fatigue units‘), meeting the Oxford criteria for CFS and having no exclusionary conditions that suggest organic dysfunction, would appear to be very small indeed. But even patients excluded under the rubric of the Oxford criteria from *research*, will now be exhorted to ‘try’ CBT and/or GET in a *clinical* context, because of the unsafe claims of the PACE trial.

Another major discrepancy in the PACE trial that I wish to specifically highlight here is that one of the treatments, ‘Adaptive Pacing Therapy’, bore no resemblance to the strategy of ‘pacing’, specifically adopted by ME patients and reported as being helpful by them in charity surveys. ‘Pacing’ as reported in these surveys is merely an autonomous flexible management strategy utilised by patients with ME in order to cope with the limitations of the illness, like sufferers of other chronic impairments. The PACE trial’s ‘Adaptive Pacing Therapy’ was not autonomous, being therapist led, and imposed a regime upon the patient similar to the GET treatment. This has specific iatrogenic potential in that, informed by the claims of PACE, patients may be told by health care professionals that an autonomous, flexible self-management strategy that is common in patients with chronic impairments, that has been found to be useful in ME/CFS, must not be practised, on the incorrect findings of a trial that did not even study the correct type of 'pacing' in the first place.

In light of the extremely complex and serious problems of confounding inherent in this trial, it is of serious issue that unsafe claims of safety and efficacy of CBT/GET as treatments for ME or CFS were made by the PACE authors and supporters, to the point that iatrogenic harm could be caused to patients because of a resulting lack of understanding, by medics and ancillary staff, misinformed by such unsafe claims, of both the neurological and other physiological impairments in at least some patients given such diagnoses, and the abnormal physiological response to exertion that appears to be a key feature in those patients.

I also draw your attention to your colleague Zoe Mullan's comment to me in our email correspondence: "We were not aware of any objections to this study". I am very concerned about this as objections to the PACE trial have been publicly mounted, and indeed have been responded to (though in eventuality, not satisfactorily) by authors of the trial, some years prior to publication.

At the very least, a much more detailed discussion of limitations to this study should have been undertaken that took into account the concerns that were raised. In the circumstances and to ensure patient safety, I now believe that the article should be retracted, and the claims that CBT and GET have been found to be safe in ME and/or CFS should be publicly corrected. I must ask that you keep to your promise that “*we will invite the critics to submit versions of their criticisms for publication and we will try as best as we can to conduct a reasonable scientific debate about this paper*“ made by you on the ABC radio programme 'The Health Report'. I consider myself as one of those ‘critics’. Indeed, I believe a full and public good faith investigation of my own and others complaints need to be undertaken by you and other parties, as appropriate.

In addition, I believe there should be an unreserved public apology issued to all the ME community and their advocates who have raised legitimate and substantive concerns, in various ways, about the problems in the PACE trial, for the prejudicial misrepresentation of their concerns and motivations, made by you on the ABC radio programme 'The Health Report', in which you made the following comments:

http://www.abc.net.au/rn/healthreport/stories/2011/3192571.htm

"...the criticisms about this study are a mirage, they obscure the fact that what the investigators did scrupulously was to look at chronic fatigue syndrome from an utterly impartial perspective."

"Not this kind of orchestrated response trying to undermine the credibility of the study from patient groups but also the credibility of the investigators and that's what I think is one of the other

alarming aspects of this. This isn't a purely scientific debate; this is going to the heart of the integrity of the scientists who conducted this study."

"...indeed in a few examples allegations have been made to professional authorities, the General Medical Council here in the UK about the work of these scientists on the basis of the flimsiest and most unfair allegations. And indeed the study costs $4 million pounds to undertake but the allegations and the freedom of information requests and the legal fees that have been wrapped up over the years because of these vexatious claims has added another 750,000 pounds of taxpayers' money to the conduct of this study."

"Indeed, and I think this is where one sees a real fracture in the patient community. One is seeing a very substantial number of patients very willing to engage in this study, desperate to get good evidence on which to base their future treatment but one sees a fairly small, but highly organised, very vocal and very damaging group of individuals who have I would say actually hijacked this agenda and distorted the debate so that it actually harms the overwhelming majority of patients."

"Well what we're doing right now is waiting for the formal response from the authors to this 43 page attack on their integrity and the study and the request for a retraction. We plan to publish their response to that attack, we will invite the critics to submit versions of their criticisms for publication and we will try as best as we can to conduct a reasonable scientific debate about this paper. This will be a test I think of this particular section of the patient community to engage in a proper scientific discussion."

These prejudicial comments should also be retracted. They are inappropriate and inaccurate, and sadly indicate a possible bad faith on your part from the offset, and this is an unusual and extremely worrying response from the editor of a key medical journal to the reasonable concerns that have been raised, in good faith, by a vulnerable patient community and others supporting them. I cannot emphasise enough that the concerns related by myself and others relate specifically to the risks to safety of patients, and our concern to prevent those: this is the motivation for my own actions here.

In addition, please note that I am, here, formally, repeating my request, made to Zoe Mullan initially, that peer review documentation be made accessible to me under the Freedom of Information Act. I understand that the usual procedure under this Act applies. I am concerned that no response has been given to my original request, made in early March.

Please be aware that, in the interests of transparency and accountability, I will be publicising this email, and I may publish the responses I receive.

Yours sincerely

Angela Kennedy