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Dear Dr Spencer

In your acknowledgement of my letter of 15th April 2016 to Dr Richard Horton, you write: *"We have received, considered and discussed your letter. We recognise that scientific findings can be a matter for debate, but disagreement, however intense, is not grounds for retraction of an article".*

In the light of the extensive international criticism of the PACE trial, I regard this as an unsatisfactory reply and ask you to reconsider.

My letter calling once again for a retraction of the PACE article is not about a "disagreement": it is a critique alerting editors of The Lancet to basic errors of fact and to misuse of statistics by the PACE PIs.

The article you published in The Lancet in 2011 promotes the use of a non-effective intervention. You will recall that one of the PACE PIs, Professor Michael Sharpe, conceded this on 18th April 2011 when he said on air: *"What this trial wasn't able to answer is how much better are these treatments than really not having very much treatment at all".*

There can be no doubt that the PACE trial did not fulfil its objective, which was to demonstrate the effectiveness of CBT/GET in "curing" ME, and that (as confirmed on 26th March 2016 by Rebecca Goldin, Director of STATS.org and Professor of Mathematical Sciences at George Mason University in Fairfax, Virginia): "*flaws in this design were enough to doom its results from the start"* (http://www.stats.org/pace-research-sparked-patient-rebellion-challenged-medicine/).

The many flaws were pointed out to you in my formal complaint of 28th March 2011: some of these were that the entry requirements and the primary outcome

thresholds were changed after the trial had begun; it failed to report on its primary outcome measures as set out in the protocol; PIs relied upon the subjective reports of participants because the use of actometers was dropped and the few remaining objective measures of function failed to demonstrate any benefit from the PIs' favoured interventions; there was an absence of blinding; it was not, as advertised, a randomised controlled trial -- there was no control group, and participants were not made aware of the conflicting interests of the investigators; astonishingly, it was possible for a participant to leave the trial with a lower physical function score and a higher fatigue score than their entry score, but still be classed as "recovered".

That is a travesty of science, a tragedy for patients and is tantamount to fraud.

The accompanying Comment by Bleijenberg and Knoop (approved before publication by the Chief PI Professor Peter White) erroneously claimed a 30% recovery rate but, even though one of your senior editors promised it would be removed, the error remains uncorrected.

For the last five years the PACE study has been totally discredited by the international community of scientists: for the selective results you published to remain in the literature to be quoted uncritically by others continues to risk more iatrogenic harm.

A key issue is that the PACE PIs did not predicate their study on what was already known and published about "CFS/ME"; on the contrary, they chose to ignore the existing evidence-base of over 5,000 papers, including one by the Chief PI himself, who had already demonstrated that *"Immunological abnormalities are commonly observed in CFS…. Altered cytokine levels, whatever their origin, could modify muscle and or neuronal function…. Concentrations of TGF-β1 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-α which was still present three days later, and this only occurred in the CFS patients….TGF-β was grossly elevated when compared to controls before exercise….The pro-inflammatory cytokine TNF-α 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 (TGFβ), whereas more intense exercise may induce pro-inflammatory cytokine release (TNF-α) in patients with CFS"* (White PD et al: JCFS 2004:12(2):51-55). This important information was withheld from participants and therapists alike and there seems to have been a disregard of safety for GET participants, even though the Chief PI was well aware that <u>three days after exercise</u>, TNFα remains elevated and that this probably accounts for the "*sickness behaviour*" and "*weakness, malaise, listlessness and inability to concentrate".*

Instead of following best practice of ensuring as homogenous a group of participants as possible, the PIs intentionally broadened their case definition: indeed, on 12th May 2004 it was minuted that the Parliamentary Under Secretary of State at the

Department of Health, Dr Stephen Ladyman, informed an All Party Parliamentary Group that doctors were being offered financial inducements to persuade patients who did not have "CFS/ME" to enter the PACE Trial.

Furthermore, after The Lancet had published selective results and despite having obtained ethical and financial approval to study "CFS/ME", the Chief PI himself wrote to Richard Horton saying that the PACE study*: "does not purport to be studying CFS/ME but CFS defined simply as a principal complaint of fatigue".*

Moreover, despite apparently screening for psychiatric disorders, the authors reported a 47% prevalence of mood and anxiety disorders at baseline, with a near equivalent use of antidepressants (41%). A 47% prevalence of mood and anxiety disorders is not compatible with results published by others. Such figures in the PACE Trial cohort confirm inherent problems with the chosen entry criteria (the Oxford criteria, partially funded by the Chief PI himself), which specifically include those suffering from affective disorders.

How can a clinical trial which intentionally ignored the existing evidence-base of the disease supposedly being studied have been eulogised by Richard Horton without bringing opprobrium upon The Lancet? As pointed out in my last letter, Dr Horton is on record as saying: *"the paper went through peer review very successfully, it's been through endless rounds of peer review and ethical review so it was a very easy paper for us to publish"*—though how it went through endless rounds of peer review when you acceded to Professor White's demand that it be fast-tracked has never been established.

Does The Lancet really regard publishing such a study as complying with its stated "*moral imperative to empower research"* so that *"medicine can serve, and transform society, and positively impact the lives of people"*? (www.thelancet.com/about-us). The Lancet also claims that it seeks *to "influence decision makers around the world"*; that it does so is borne out by the adoption of the disproved behavioural model of ME as UK Government health policy which is promulgated by the DoH, the DWP, NICE, the MRC and by numerous insurance companies for which the PACE PIs work.

As a consequence of the PACE article and of the exaggerated reporting of its alleged success, people with ME continue to suffer appallingly, either through being compelled to undergo CBT and GET (even though GET further stresses a system that is already exhausted) and/or by having their benefits removed or reduced unless they participate in a Work Related Activity Group (WRAG). Their suffering has been protracted and in many instances, it has been unbearable, resulting in a higher rate of suicide in ME than in other medical disorders, as found by the UK ME Association.

Your Lancet manifesto claims the *"Highest standards for medical science"* and that you "*select only the best papers for their quality of work"*; it also claims that *"Improving lives is the only end goal"* but you cannot be unaware of the growing international consensus which dismisses the PACE trial thus: *"It seems that the best*

we can glean from PACE is that study design is the essential to good science" (Goldin *supra*).

You will recall that in my last letter, I drew your attention to the comments of experts who have examined the PACE study, who all concur that it is "*fraught with problems"*: Ronald Davis, Professor of Biochemistry and a well-known geneticist at Stanford University said: *"I'm shocked that The Lancet published it….The PACE study has so many flaws… that I don't understand how it got through any kind of peer review"*; Jonathan Edwards, Professor Emeritus of connective tissue medicine from UCL, said: *"It's a mass of un-interpretability to me…Within the circle who are involved in this field, it seems there were a group who were prepared to all …agree that PACE was wonderful. But all the issues with the trial are extremely worrying, making interpretation of the clinical significance of the findings more or less impossible"*, and Bruce Levin, Professor of Biostatistics at Columbia University and an expert in clinical trial design, said post-protocol changes inevitably raised questions about interpretability of the results: *"I have never seen a trial where eligibility requirements…alone would qualify some patients for having had a successful treatment….I find it nearly impossible that a trial's data monitoring committee would have approved such a protocol problem if they were aware of it"*.

In contrast to the well-publicised belief of the Chief PI and hence to the message of the PACE study that you published (namely, that "CFS/ME" is a behavioural disorder that is amenable to cognitive re-structuring and graded aerobic exercise), I now draw your attention to a recent Editorial by Professor Jonathan Edwards who, with co-authors from France and Australia, highlights important areas for urgent research in ME, especially brain imaging, NK cell function, cytokine shifts, autoantibodies for neuronal components, and continued exploration of the dysregulation of autonomic and endocrine signalling systems (dysregulation of which is prominent in ME/CFS), as well as physiological responses to exertion. Of paramount importance, say these authors, is the requirement for all raw data to be made available, even if null or unpublished, so that meta-analyses can be accurate (http://dx.doi.org/10.1080/21641846.2016.1160598) .

The evidence is now overwhelming that the PACE study failed; indeed, the decision of the PIs to challenge the ICO's ruling that fully anonymised data from the trial should be released only serves to confirm the widely-held belief that without significantly revised *post-hoc* end-points, the trial would have produced a null result.

By refusing to retract the PACE paper, you remain in clear breach of your own standards.

Should this not be of concern to The Lancet's editors?

Yours sincerely

Malcolm Hooper