

Response to “Commentary on Cochrane Corner”

T Chalder<sup>1</sup>, PD White<sup>2</sup>, M Sharpe<sup>3</sup>

1 Academic Department of Psychological Medicine, King’s College London, London, UK

2 Wolfson Institute of Preventive Medicine, Barts and the London School of Medicine and Dentistry,  
Queen Mary University of London, UK

3 Psychological Medicine Research, University of Oxford Department of Psychiatry, Oxford, UK

## Abstract

Science benefits from criticism. We support the right of colleagues to criticise our work, as Mitchell has done in his commentary on the PACE trial of therapies for people with chronic fatigue syndrome (CFS), which we led. However we also believe that criticism is only useful if it is based on an accurate account of such work. In our view, Mitchell's criticisms are, not based on an accurate account of the research. We address the main criticisms and conclude that both graded exercise therapy (GET) and cognitive behaviour therapy (CBT) are useful and safe treatments for people with CFS.

In his recent article, Mitchell has made a number of criticisms of the PACE trial (Mitchell, 2017). However, the criticisms are based on inaccurate information and are consequently misleading.

1. Mitchell suggested that a re-analysis of some of the data related to the PACE trial found the effect sizes to be smaller than those which we originally reported (White et al, 2011). This is incorrect. He has confused the effect size reported in the main trial paper (which was calculated using scores of the two primary outcomes) with results of a secondary analysis of the data. The latter reports the proportions of participants meeting various criteria for recovery (see below) (White et al, 2013, Wilshire et al, 2017).

2. Mitchell implies that we only released certain results, such as objective metrics from the 6-minute walking test data, as a consequence of data release that was forced upon us following an Information Tribunal in 2016 (Mitchell, 2017). These results were in fact published in our main results paper five years earlier (White et al, 2011).

3. Mitchell states: "...it is also alleged that the investigators (perhaps inadvertently) influenced participants' self-reports with indiscriminate encouragement in newsletters sent out during the trial" (Mitchell, 2017). It has indeed been alleged, but the allegation is incorrect. As in all well-run trials, we engaged with participants by sending them regular newsletters about trial progress. As part of that, we included quotations of positive feedback about the trial and the treatments that they had received. The newsletters (which readers can review at

<http://www.wolfson.qmul.ac.uk/images/pdfs/participantsnewsletter3.pdf>) did not name any

treatment and included positive quotations about all four treatments being evaluated in the trial.

We also measured participant expectation of their allocated treatment after they had been informed of it and, as reported in the main paper, most participants considered adaptive pacing therapy (APT) and GET to be most likely to help them, whereas the trial found CBT and GET were most effective (White et al, 2011).

4. Mitchell says “It is also alleged that the investigators switched their own scoring methods mid-trial” (Mitchell, 2017). As is common practice in most trials, and as we agreed to do in our original protocol (White et al, 2007), the outline analysis plan was reviewed and a detailed analysis plan was written and subsequently published (Walwyn et al, 2013). This was approved by two independent oversight committees before any outcome data was analysed. The detailed plan used the same primary outcomes. The change Mitchell is referring to was in the scoring method of one of the primary outcome measures. A binary (0,0,1,1) scoring method was changed to a Likert scoring method (0,1,2,3), in order to provide a more accurate measure of efficacy. This change and the reason for it were clearly reported in the papers (White et al, 2011; Walwyn et al, 2013). Re-analysing the data using the binary scoring made no difference to our conclusions that both CBT and GET are effective treatments (Goldsmith et al, 2016).

5. Mitchell criticises us and one of our Universities for not releasing more data and earlier. This criticism is misleading. We have already explained that we simply did not have participants’ consent to release their individual patient data (White et al, 2016). This is because the public release of data, which has now occurred as a result of an Information Tribunal, and which Mitchell promotes in providing a link, has been explicitly proscribed by our Research Ethics Committee. We have however shared data with other researchers, including a Cochrane Collaboration team, who agreed to keep the data confidential.

6. Finally, Mitchell suggests that a re-analysis of the proportions of participants meeting criteria for recovery suggest that few participants recovered with CBT and GET (Wilshire et al, 2017). We have already pointed out that our recovery (as opposed to improvement) estimates depended on assumptions (White et al, 2013; Sharpe et al, 2017). The Wiltshire reanalysis simply makes different assumptions, using more stringent thresholds to determine recovery. That having been said, our recovery rates were similar to those found in previous studies (22% recovered after CBT and GET) (Sharpe et al, 2017).

We agree with Mitchell that there are lessons to be learnt from the PACE trial, but they are not the lessons he suggests:

1. Mitchell says: “First and foremost, it is imperative for researchers to publish studies in the most open and transparent manner possible.” In fact almost all our papers were published with open access, and we have responded to scientific queries and criticisms appropriately and repeatedly in papers cited here, in journal correspondence, and in over one hundred frequently asked questions available on the trial website (<http://www.wolfson.qmul.ac.uk/current-projects/pace-trial>). We have also shared data when ethically possible (White et al, 2016).
2. Mitchell says: “A second lesson is that clinicians and researchers should work more closely with patients...” In fact a patient charity and a patient were involved early on in designing the trial, and were full members of our trial steering and/or trial management committees (White et al, 2015).

Mitchell says: “The third lesson is that, to promote acceptability, psychosocial treatments should be integrated into medical care.” In fact the PACE trial treatments were integrated with medical care and all participants in the PACE trial received appropriate medical care provided by CFS specialists. We suggest that the most obvious lesson from our experience of the PACE trial is that science can sometimes provide answers to questions that are not popular with everyone (Lancet, 2011; Hawkes, 2011, Wessely, 2015, Sharpe et al, 2016). However such answers should stand or fall by independent replication, not by unreasonable criticism and demands for retraction. We note that the PACE trial replicated findings from many earlier randomised controlled trials, many of which were conducted by researchers in different countries (Castell et al 2011; Larun et al 2016). We look forward to further robust studies that the conclusion of the PACE trial that CBT and GET are superior to pacing and specialist medical care alone in improving both fatigue and physical functioning in patients with CFS.

## Conflicts of Interest

TC and MS have received royalties from academic publishers. PDW has done voluntary and paid consultancy work for the United Kingdom government and a reinsurance company.

## References

Castell BD, Kazantzis N, Moss-Morris RE (2011). Cognitive behavioral therapy and graded exercise for chronic fatigue syndrome: a metaanalysis. *Clinical Psychology: Science and Practice*, 18: 311–24.

Goldsmith KA, White PD, Johnson AI, Chalder T, Sharpe M (2016). The PACE trial: Exploratory analysis of primary fatigue outcomes using bimodal rather than continuous Likert type scoring on the Chalder fatigue scale.

[http://www.wolfson.qmul.ac.uk/images/pdfs/pace/PACE\\_bimodal\\_CFQ\\_analysis\\_final\\_8\\_Sept\\_2016.pdf](http://www.wolfson.qmul.ac.uk/images/pdfs/pace/PACE_bimodal_CFQ_analysis_final_8_Sept_2016.pdf)

Hawkes N (2011). Dangers of research into chronic fatigue syndrome. *BMJ* 342: d3780.

The Lancet. 2015 Editorial: Patients' power and PACE. 377(9790): 1808

Larun L, Brurberg KG, Odgaard-Jensen J, et al (2016) Exercise therapy for chronic fatigue syndrome. *Cochrane Database of Systematic Reviews*, 6: CD003200. doi: 10.1002/14651858.CD003200.pub6.

Mitchell AJ (2017). Controversy over exercise therapy for chronic fatigue syndrome: key lessons for clinicians and academics. *BJPsych Advances* 23: 145–148 doi:10.1192/apt.bp.116.016261

NICE (2007). National Institute for Health and Clinical Excellence. Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (or Encephalopathy): Diagnosis and Management of CFS/ME in Adults and Children (Clinical Guideline CG53).

Sharpe M, Goldsmith KA, Johnson AL, Chalder T, Walker J, White PD (2016). Patient reaction to the PACE trial – Authors’ reply. *Lancet Psychiatry* 3(2): e8-9. doi: 10.1016/S2215-0366(16)00018-3.

Sharpe M, Chalder T, Johnson AL, Goldsmith KA, White PD (2017). Do more people recover from chronic fatigue syndrome with cognitive behaviour therapy or graded exercise therapy than with other treatments? *Fatigue: Biomedicine, Health & Behavior* 5: 57-61. DOI:

<http://dx.doi.org/10.1080/21641846.2017.1288629>

Walwyn R, Potts L, McCrone P, et al (2013). A randomised trial of adaptive pacing therapy, cognitive behaviour therapy, graded exercise, and specialist medical care for chronic fatigue syndrome (PACE): Statistical analysis plan. *Trials* 14: 386. DOI: 10.1186/1745-6215-14-386

Wessely S (2015) The PACE Trial for chronic fatigue syndrome: Choppy seas but a prosperous voyage. Available at: <http://www.nationalelfservice.net/other-health-conditions/chronic-fatigue-chronic-fatigue-syndrome-choppy-seas-but-a-prosperous-voyage/>

White PD, Sharpe MC, Chalder T et al (2007). Protocol for the PACE trial: 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. *BioMed Central Neurol* 7: 6 <http://www.biomedcentral.com/1471-2377/7/6>

White PD, Goldsmith KA, Johnson AL et al (2011). Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet* 377: 823-36.

White PD, Johnson AL, Goldsmith K, Chalder T, Sharpe MC (2013). Recovery from chronic fatigue syndrome after treatments given in the PACE trial. *Psychol Med* 43: 2227-235.

doi:10.1017/S0033291713000020

White PD, Chalder T, Sharpe M (2015). The planning, implementation and publication of a complex intervention trial for chronic fatigue syndrome: the PACE trial. *BJPsych Bulletin* 39: 24-27.

doi:10.1192/pb.bp.113.045005

White PD, Chalder T, Sharpe M (2016). Releasing patient data from the PACE trial for chronic fatigue syndrome. In: *BMJ Blogs*, 10 October. Available at: <http://blogs.bmj.com/bmj/2016/09/22/peter-white-et-al-releasing-patient-data-from-the-pace-trial-for-chronic-fatigue-syndrome/>

Wilshire C, Kindlon T, Matthees A, McGrath S (2017). Can patients with chronic fatigue syndrome really recover after graded exercise or cognitive behavioural therapy? A critical commentary and preliminary re-analysis of the PACE trial. *Fatigue Biomed Health Behavior* 5: 43-56.