

## The PACE Trial Controversy: A Summary

This briefing was prepared by a Science for ME working group of patients, most with a background in science and mathematics. The authors, including Tom Kindlon, Sean Kirby and Graham McPhee, have published over twenty papers and letters of expert commentary on the PACE trial and related matters in peer-reviewed journals such as The Lancet and the British Medical Journal.

*White et al. conclude that they stand firmly by the findings of the PACE trial, presumably because of their inability to understand its basic flaws. As has been suggested by others, the flaws are so egregious that it would serve well in an undergraduate textbook as an object lesson in how not to design a trial.*

**Emeritus Professor of Medicine Jonathan Edwards<sup>1</sup>**

### Background

In 2007, NICE recommended graded exercise therapy (GET) and cognitive behavioural therapy (CBT) for patients with chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME).<sup>2</sup> But this guideline was based on weak evidence from small trials and so the much larger PACE trial was designed as a definitive test of these therapies.<sup>3</sup>

PACE had over 600 patients, cost £5 million,<sup>4</sup> and was taxpayer-funded, mostly by the Medical Research Council. Uniquely for a clinical trial, the Department of Work and Pensions also contributed to it.<sup>3</sup>

PACE used subjective outcomes as its primary measures, but also included objective outcomes such as aerobic fitness. In clinical trials, subjective measures – patients' self-ratings of symptoms – are influenced not only by how they actually feel but by their expectations of the treatment and their wish to please the experimenter. This is why drug trials use identical-looking pills to keep patients 'blind to' (ignorant of) whether they are receiving the new drug or the old one (or a placebo). In PACE, this 'blinding' was not possible because of the nature of the treatments, and so the objective measures were crucial.

Another important feature of the trial was that the researchers prespecified how they would analyse its data – an established method to avoid the later 'cherrypicking' of favourable results.

During the year-long trial, all of the patients received standard medical care. They were randomly split into four groups. Three of the groups received an additional therapy – GET, CBT or 'adaptive pacing therapy' – and the fourth, a comparison group, received none.

From 2011 onward, PACE's findings appeared in *The Lancet* and other journals.<sup>3</sup> The researchers reported that in the CBT and GET groups, approximately 60% of patients 'improved' and 22% 'recovered' – more than for the comparison groups.<sup>3,5</sup> The treatments were said to be moderately effective, and safe.<sup>3</sup>

These claims had two consequences. First, NICE left its recommendations for CBT and GET in place.<sup>6</sup> Second, widespread promotion of the trial's success to the public, clinicians and academics<sup>7,8,9</sup> led to uncritical acceptance of the explicit assumption behind PACE's CBT and GET: that CFS patients are just deconditioned and fearful of exertion, and can recover if they increase their activity and focus less on their symptoms.<sup>3</sup>

## Why has PACE been criticised?

*'I'm shocked that the Lancet published it...The PACE study has so many flaws and there are so many questions you'd want to ask about it that I don't understand how it got through any kind of peer review.'*

**Ronald W. Davis, Professor of Biochemistry and Genetics at Stanford University<sup>10</sup>**

ME/CFS has been shown to be at least as disabling as multiple sclerosis,<sup>11</sup> with roughly a quarter of patients bedbound or housebound<sup>12</sup> – many for decades – and an estimated recovery rate in adults of only 5%.<sup>13</sup> Recent, major research reviews of the biomedical literature commissioned by the US government have emphasised that ME/CFS is not psychological, but is a severely debilitating, multi-system, physical disease.<sup>14,15</sup>

PACE's claims ran counter to patients' knowledge and lived experience, leading some to examine the trial's methods. Those who did found two main problems, both serious.

### **1. The objective results contradicted the subjective results**

Objective results were poor.<sup>16</sup> The GET group outperformed the no-therapy comparison group on a six-minute walking test<sup>3</sup> but PACE's authors did not make clear what a bad result this was: after a year of therapy, the GET group's increase in walking speed was less than half that achieved in *three weeks* in a sample of Class II chronic heart failure patients receiving graded exercise.<sup>17</sup> In fact, the GET group's walking speed was only about half that of a healthy age-matched sample.<sup>18</sup>

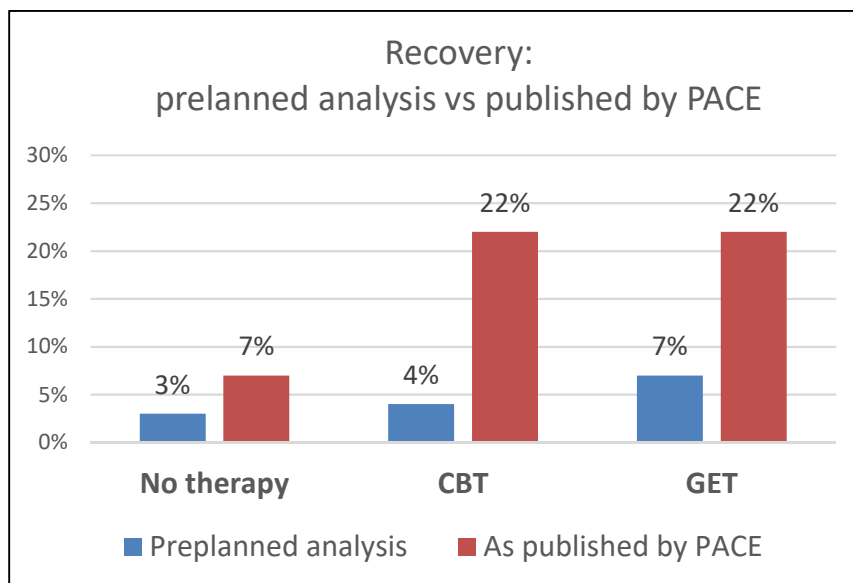
In PACE, aerobic fitness – and therefore probably also activity levels – did not improve in any group, but these results were not published until four years after the main paper.<sup>19</sup> Other objective outcomes, whose publication was also delayed, showed that the therapies did not return patients to work or reduce their uptake of sickness benefits.<sup>20</sup>

## 2. The planned analyses for improvement and recovery had been abandoned

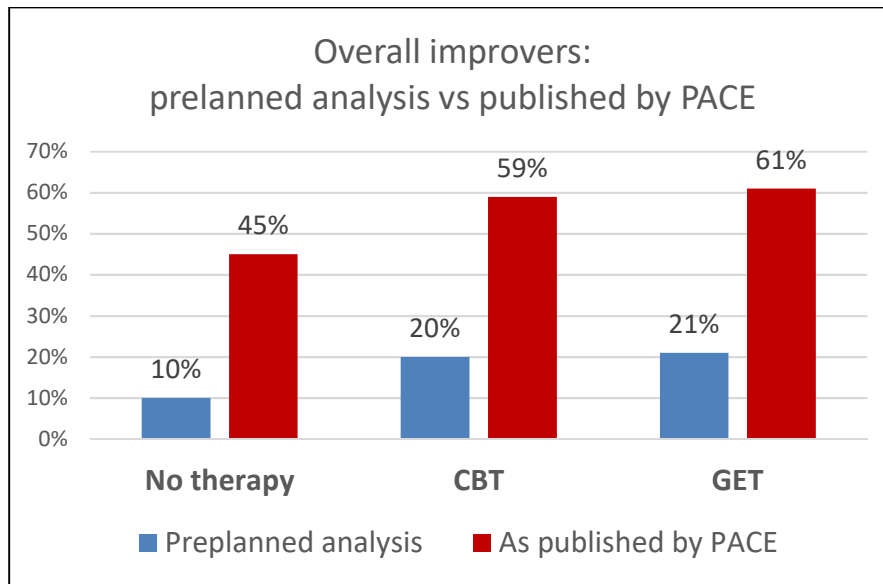
After the trial had finished, the PACE authors discarded their originally planned definitions for improvement and recovery and replaced them with laxer ones that would inevitably inflate those figures.<sup>3,5</sup> The new thresholds were so low that *patients could get worse on a scale of fatigue or activity levels than when they entered the trial and yet be considered to have entered a 'normal range' and to have recovered.*<sup>21</sup>

Queen Mary University London (QMUL), PACE's data custodian, refused to provide critics with either the study's pre-planned outcomes or the relevant raw data to calculate the figures themselves.<sup>22</sup> QMUL spent over £200,000<sup>23</sup> unsuccessfully fighting a Freedom of Information Act request to provide the data.<sup>24</sup>

Despite the limited data finally released by QMUL, independent researchers were able to carry out statistical analyses almost identical to those prespecified by PACE.<sup>16</sup> The percentage of patients who 'recovered' fell from 22% for CBT and GET to 7% or below in each group, and showed no statistically meaningful difference between groups: that is, CBT and GET did not help patients recover.



The 'improvement' results were also far less impressive. 'Overall improvement' rates (requiring specific levels of improvement on both fatigue and physical function) fell from roughly 60% for CBT and GET to roughly 20%, compared to 10% for the no-therapy group – again, not a statistically meaningful difference and so a 'null' result, indicating that the treatments had no effect.<sup>16</sup> For fatigue on its own, only the CBT group did better than the no-therapy group; and for physical function on its own, only the GET group did so. But the results only just scraped into being statistically meaningful in each case.



If these weak and null results had been published in 2011, it seems likely that NICE would have withdrawn its recommendation of the use of CBT and GET for ME/CFS.

### Why was PACE's failure not acknowledged?

PACE was a nonblinded trial with unimpressive or null results on its subjective measures, when analysed according to its prespecified methods. Its objective measures showed that CBT and GET did not improve patients' fitness or ability to work. PACE's long-term follow-up results were also null.<sup>16,25</sup>

The trial has, however, been defended vigorously by its researchers and their supporters.<sup>26,27</sup> Crucially, they do not accept the key criticism that the nonblinded design of the trial favoured CBT and GET. They argue that patients' pre-trial expectations of success did not particularly favour those two therapies.<sup>3</sup> However, any undue influence on self-ratings would have arisen *during* the many treatment sessions in the trial, in which CBT and GET patients alone were told that their treatments were 'powerful' and 'effective' and that there was nothing to stop them getting well.<sup>28,29</sup>

The PACE authors have claimed that reviews by the Cochrane organisation of other CBT and GET studies confirm PACE's results<sup>30</sup> – but the studies in those reviews are also nonblinded trials with subjective primary measures.<sup>31, 32</sup>

### What patients need now

PACE's serious flaws are increasingly widely recognised;<sup>33,34</sup> it is even being used as a teaching example of bad scientific practice in a number of universities.<sup>35,36</sup> In addition to a

petition from more than 12,000 individuals – mostly patients<sup>37</sup> – over 90 scientists and clinicians and more than 50 patients’ groups worldwide have written to Psychological Medicine demanding retraction of the misleading ‘recovery’ results,<sup>38</sup> and The Lancet has been asked to correct the ‘normal range’ results.<sup>39</sup> The controversy has reached the British and international press.<sup>40-44</sup>

Patients want this recognition of PACE’s failure to turn into action, and their immediate concern is that GET is actively dangerous. PACE reported no more harm to patients in the CBT or GET groups than in the comparison groups,<sup>3</sup> but the lack of increase in fitness in any group in the trial suggests that most patients may not have increased their activity enough to trigger a reaction.<sup>18</sup> If patients in a drug trial do not achieve the required dose, the results do not help to evaluate drug safety: PACE’s safety data are similarly uninterpretable.

But ME/CFS’s cardinal symptom is that patients get worse with exercise.<sup>14</sup> Physiology researchers warn that graded exercise would be expected to harm ME/CFS patients, regardless of the skill of the therapist.<sup>45</sup> In surveys, more than 2,000 out of 4,000 patients, including children, reported being made worse by GET.<sup>46</sup> Some patients tell of being made bedbound.<sup>47</sup> On a national scale, the level of harm is likely to be considerable.

*Robert was 12 when he first started [NHS] graded exercise therapy. His mother [explained]: ‘Robert was moderately ill when the physio began but became severely ill and required a wheelchair after a few months... After just a few months, he lost the ability to walk... The physiotherapist wouldn’t accept they were causing the harm and blamed my son for not trying hard enough, saying he didn’t want to get better; they would not accept that there was anything physically wrong with him... He had a fit in the pool where they were doing the exercises, which the neurologist later said was caused by extreme pain. Eventually, we had to get a charity to intervene so that we could stop the graded exercise. My son is now 21 and is still severely ill and housebound.*

**Report in The Independent<sup>48</sup>**

Contrary to the claims of the PACE researchers and their supporters, PACE’s results show that CBT and GET do not work for this disease. In the US, the Centers for Disease Control recently withdrew its recommendation of these therapies for ME/CFS.<sup>49</sup> Patients urgently want NICE to do the same, before more harm is caused.<sup>50</sup>

This would leave patients without any recommended treatments, due to a longstanding failure of government bodies in the UK and abroad to fund biomedical research at meaningful levels.<sup>51</sup> Patients need the British government to now fund a proactive, coordinated, urgent

biomedical research strategy for ME/CFS in line with the scale and seriousness of the problem.

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