The PACE trial in chronic fatigue syndrome

In their randomised trial of treatments for patients with chronic fatigue syndrome, Peter White and colleagues (March 5, p 823) defined a clinically useful difference between the means of the primary outcomes as “0.5 of the SD of these measures at baseline, equating to 2 points for Chalder fatigue questionnaire and 8 points for short-form 36”. They cite achieving a mean clinically useful difference in the graded exercise therapy or cognitive behaviour therapy groups, compared with specialist medical care alone, as evidence that these interventions are “moderately effective treatments”.

The source for this definition of clinically useful difference states that such a method has a “fundamental limitation”: “estimates of variability will differ from study to study...if one chooses the between-patient standard deviation, one has to confront its dependence on the heterogeneity of the population under study”. In White and colleagues’ study, we do not have heterogeneous samples on the Chalder fatigue questionnaire and short-form 36 physical function subscale, since both are used as entry criteria.1

Patients had to have scores of 65 or less on short-form 36 to be eligible for the study.1 However, most, in practice, would probably need to have scores of 30 or more to be able to participate in this clinic-based study. Indeed, only four of 43 participants in a previous trial of graded exercise therapy scored less than 30.2 Guyatt and colleagues3 suggest that “an alternative is to choose the standard deviation for a sample of the general population”, which White and colleagues have given as 24.4 An SD of 24 gives a clinically useful difference of 12; both graded exercise therapy and cognitive behaviour therapy fail to reach this threshold. Whether they “moderately improve outcomes”, as claimed,1 is therefore questionable.

Much has been made of the “recovery” achieved by some participants in Peter White and colleagues’ PACE trial,1 one of the authors having stated to the media that “twice as many people on graded exercise therapy and cognitive behaviour therapy got back to normal”2 and the accompanying Comment stating that, by use of a “strict criterion” for recovery, “the recovery rate of cognitive behaviour therapy and graded exercise therapy was about 30%”.3

Although the trial protocol4 does give a strict definition for recovery, this information is omitted from the published paper, which instead refers to physical function and fatigue in the “normal range”. Whether the values given are indicative of normal function is open to question, however. For instance, although a score of 60 or more on the short-form 36 (SF-36) physical function subscale and of 18 or less on the Chalder fatigue questionnaire are characterised as being in the “normal range” by White and colleagues, and as “recovery” in the accompanying Comment, an SF-36 physical function score of 65 was low enough for a patient to be included in the trial to begin with. Additionally, the above definitions for recovery and normal range would not even have qualified as being a positive outcome (75 or more on SF-36, bimodal fatigue scale score 3 or less) as published in the original protocol. Data on increases in baseline scores, the other positive outcome measure, are not given.

Also in question is how White and colleagues arrived at their reduced thresholds, since the trial protocol states that an SF-36 score of 70 is one SD below the mean of the UK adult population, but in the published paper this figure drops to 60 without explanation.

I am a CFS patient.

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1 White PD, Goldsmith KA, Johnson AL, et al, on behalf of the PACE trial management group. 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: 823-36.


I am chair of a myalgic encephalomyelitis support and advice group—an unpaid voluntary position.

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I am concerned by the change in assessment method between the published results of the PACE trial and the trial protocol. Seven secondary outcomes were not reported and there were changes in several of the measures that were reported. 

In particular, the protocol stated that those with short-form 36 physical function subscale scores of 65 or less would be deemed ill enough to participate, and that those with scores of 85 or more would be regarded as “recovered.” However, the authors have questionably defined “normal” as a score of 60 or more, based on general population scores which did not exclude those reporting chronic illnesses. In the cited study of working-age adults, the mean physical function score for those aged 75-84 years, including those with long-term health problems, was 57.9. The lack of objective data, such as hours employed or actometer results, is problematic, since Wiborg and colleagues showed that improvements on questionnaires are not reflected in an increase in activity, as would be expected if the patients had more energy.

The only significant difference between treatments for the 6-min walking test was for graded exercise therapy. But the increase in walking distance is small when compared to the distance walked by healthy elderly people (mean age 65 years), which was shown to be 631 m (SD 93). Unfortunately, the overall results of the PACE treatments were unimpressive, and with only 41% of patients reporting “positive” change after cognitive behavioural therapy or graded exercise therapy, further biomedical research is imperative.

I declare that I have no conflicts of interest.

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1. White PD, Goldsmith KA, Johnson AL, et al, on behalf of the PACE trial management group. 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: 813–36.


I declare that I have no conflicts of interest.

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The findings of the PACE trial seem impressive, but the discrepancy between the definitions of improvement in the protocol and paper requires an explanation. In the paper “clinically useful differences” were defined as 0.5 SD changes in fatigue or physical functioning compared with baseline. However, the criteria for improvement published in the trial protocol were:

<table>
<thead>
<tr>
<th>Trial protocol</th>
<th>Final publication</th>
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<tbody>
<tr>
<td>Fatigue (bimodal Chalder scale)</td>
<td>50% reduction or score ≤3 7% reduction* or score ≤4†</td>
</tr>
<tr>
<td>Physical functioning (SF-36 subscale)</td>
<td>50% increase or score ≥7 21% increase or score ≥60</td>
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* Clinically useful difference of 2 points (0.5 SD) and mean baseline Likert score of 28.2. † Likert score of ≥18 used by the authors implies bimodal score of ≥4. I Clinically useful difference of 8 points (0.5 SD) and mean baseline short-form 36 (SF-36) physical function subscale score of ≥38.0.

Table: Definition of positive outcome/improvement in the trial protocol and the final publication.