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Dear Professor White

We write further to the publication of the PACE Trial, Lancet, 18th February.[1]

After carrying out our own collective analysis, we note that the published results appear not to have presented data relevant to certain measures detailed in the PACE protocol2,, whilst data for other measures not specified in the protocol was presented.

We are presuming that the trial received ethical permission on the basis that the promised data would be published and we would therefore appreciate the missing information itemised below. Could you please release this data either directly to ourselves or in a publicly accessible forum such as a medical journal as it may help to further inform stakeholders.

We are mindful of the cost to the taxpayer of this particular trial and out of courtesy we have copied in representatives of each of the PACE funding sources into this correspondence.

Missing data and clarifications

The bold text and bracketed numbers correspond to pp11-12 of the protocol.[2]

Primary outcome measures – Primary efficacy measures

The protocol states: '**Since we are interested in changes in both symptoms and disability we have chosen to designate both the symptoms of fatigue and physical function as primary outcomes. This is because it is possible that a specific treatment may relieve symptoms without reducing disability, or vice versa. Both these measures will be self-rated.**

The 11 item Chalder Fatigue Questionnaire measures the severity of symptomatic fatigue [27], and has been the most frequently used measure of fatigue in most previous trials of these interventions. We will use the 0,0,1,1 item scores to allow a possible score of between 0 and 11. A positive outcome will be a 50% reduction in fatigue score, *or* a score of 3 or less, this threshold having been previously shown to indicate normal fatigue [27].

The SF-36 physical function sub-scale [29] measures physical function, and has often been used as a primary outcome measure in trials of CBT and GET. We will count a score of 75 (out of a maximum of 100) or more, *or* a 50% increase from baseline in SF-36 sub-scale score as a positive outcome. A score of 70 is about one standard deviation below the mean score (about 85, depending on the study) for the UK adult population [51,52].

Those participants who improve in both primary outcome measures will be regarded as overall improvers.'

Our comment: In the published paper1, normal physical functioning is no longer given as a primary outcome measure and the 50% increase is not used. An SF-36 score of 60 or more, is claimed to be one standard deviation below the mean for the working age population, although the reference given does not appear to show this. We note that patients with an SF-36 score of 65 at baseline could participate in the trial.

We are no longer given the data on fatigue as in the protocol paper. The definition of 'fatigue caseness' (bimodal score of more than 3) given in the protocol is a validated definition of fatigue.3 Neither it or the 50% reduction are used in the final paper.

We would therefore be interested in receiving data for the three outcome measures below to clarify how many participants in each arm of the trial met the criteria defined in the protocol paper after completing treatment:

(i) 'Positive outcome' (Chalder fatigue score)
(ii) 'Positive outcome' (SF-36 PF)
(iii) 'Overall improvers'

Secondary outcome measures – Secondary efficacy measures

(1). The Chalder Fatigue Questionnaire Likert scoring (0,1,2,3) will be used to compare responses to treatment [27].

Our comment: This now appears to have become a primary measure.

(3). The CGI change scale will also be rated by the treating therapist at the end of session number 14, and by the SSMC doctor at the 52-week review.

Our comment: Not Given

(4). "Recovery" will be defined by meeting all four of the following criteria: (i) a Chalder Fatigue Questionnaire score of 3 or less [27], (ii) SF-36 physical Function score of 85 or above [47,48], (iii) a CGI score of 1 [45], and (iv) the participant no longer meets Oxford criteria for CFS [2], CDC criteria for CFS [1] or the London criteria for ME [40].

Our comment: Not Given

We would therefore be interested in receiving the data for 'recovery' as defined in the protocol paper and how many participants in each arm of the trial met the criteria specified above after completing treatment?

As CBT and GET participants are encouraged to see symptoms as "temporary and reversible" we believe this to be important "proof of concept" information.4,5

(7). The EuroQOL (EQ-5D) provides a global measure of the quality of life [39].

Our comment: Not Given

(8). The six-minute walking test will give an objective outcome measure of physical capacity.

Our comment: On average for the questionnaire data presented in Table 6, 587 results are available for nearly 92% of participants. However, for the only remaining objective outcome measure (after the dropping of actometers) comparative data is missing for nearly one third of the GET participants (31%) and nearly one quarter of the CBT participants (24%).

Were the participants for whom data was not presented different from the rest? For example, if they had lower scores at baseline and/or at 24 weeks.

(9). The self-paced step test of fitness [43].

Our comment: Not Given

(10). The Borg Scale of perceived physical exertion [44], to measure effort with exercise and completed immediately after the step test.

Our comment: Not Given

(11). The Client Service Receipt Inventory (CSRI), adapted for use in CFS/ME [31], will measure hours of employment/study, wages and benefits received, allowing another more objective measure of function.

Our comment: Not Given. We feel it is important that this data is made available as it 'allows for a more objective measure of function'.

(12). An operationalised Likert scale of the nine CDC symptoms of CFS [1].

Our comment: Likert scale data was not given. Instead all that was given was present/absent data

A composite yes/no score for the 8 or 9 (it is unclear) CDC symptoms is given, however we are only presented with a breakdown for two of the symptoms. We would like data on the other 6/7 symptoms.

Clarification sought re-Table 6:

Is the Chronic fatigue syndrome CDC symptom count based upon eight or nine symptoms? (Some will read the table as eight symptoms - as they see 'CDC symptoms' as eight - excluding fatigue.)

Criteria for the percentages given for the two symptoms given: if a participant said a symptom was "present a little", was that counted as having the symptom?

(13). The Physical Symptoms (Physical Health Questionnaire 15 items(PHQ15)) [35].

Our comment: Not Given.

Adverse outcomes

Adverse outcomes (score of 5–7 of the self-rated CGI) will be monitored by examining the CGI at all follow-up assessment interviews [49]. An adverse outcome will be considered to have occurred if the physical function score of the SF-36 [28] has dropped by 20 points from the previous measurement. This deterioration score has been chosen since it represents approximately one standard deviation from the mean baseline scores (between 18 and 27) from previous trials using this measure [23,25]. Furthermore, the RN will enquire regarding specific adverse events at all follow-up assessment interviews.

- Our comment: We note this this has not been given as per the protocol and been re-defined to be "any two consecutive assessment interviews" .
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- Additional Comments
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- We have noted that a new measure, "a clinically useful difference", was introduced in the published paper, however data on deteriorations using this measure appears to be missing?
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- In figures 2F and 2G (International CFS criteria and London ME criteria, respectively), there does not appear to be a statistically significant difference between the SMC and both GET and CBT. We would be grateful if you could supply the exact means and standard deviations for these graphs (i.e. the unadjusted data) along with the means and standard deviations for the adjusted data covered by Figure 2.

We look forward to hearing from you.

Yours Sincerely

Neil Riley for The ME Association

Jane Colby for The Young ME Sufferers Trust

Duncan Cox on behalf of West Midlands ME Groups Consortium (Herefordshire ME/CFS/FMS Group; Solihull& South Birmingham ME Support Group, Shropshire ME Group; Walsall ME Link; Warwickshire Network for ME; and Worcestershire ME Support Group)

References

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3. Chalder T, Berelowitz G, Hirsch S, Pawlikowska T, Wallace P, Wessely S, Wright D: Development of a fatigue scale. J Psychosom Res 1993, 37:147-153.

4. CBT treatment manual. PACE trial Information page. http://www.pacetrial.org/docs/cbt-therapist-manual.pdf [Last accessed: 31st March, 2011]

5. GET treatment manual. PACE trial Information page. http://www.pacetrial.org/docs/get-therapist-manual.pdf [Last accessed: 31st March, 2011]

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