**Reviewer’s report**

**Title:** Rethinking the treatment of chronic fatigue syndrome—A reanalysis and evaluation of findings from a recent major trial of graded exercise and CBT

**Version:** 0  **Date:** 13 Sep 2017

**Reviewer:** Finbarr Leacy

**Reviewer's report:**

**Major comments:**

The appropriateness of last observation carried forward (LOCF) as the primary analysis under the intention-to-treat principle should be discussed. In particular, the assumptions underpinning and potential drawbacks of the LOCF approach and should be highlighted. Ideally, a sensitivity analysis e.g. best-case, worst-case analysis would be presented. See references [1] and [2] below for useful discussion. A multiple imputation analysis under the MAR analysis might also have been appropriate had the FOIA dataset utilised by the author contained information on the additional stratification variables specified in the protocol.

Please highlight rebuttals from the original study authors as appropriate.

**Minor comments:**

Abstract, RESULTS: Replace first sentence with: "We found no statistically significant differences on protocol specified primary outcome measures - improvement in self-reported fatigue and physical functioning - between the CBT and GET groups and conventional medical care following adjustment for multiple testing"

Abstract, CONCLUSIONS: Text insertion: "The results of PACE are [potentially] not as robust as claimed.

A brief summary of the trial entry criteria as they pertain to the primary outcome measure scores would aid the reader.

Line 47: Please highlight that the change in primary outcome has subsequently been defended by the original study authors, e.g. in [3].
Line 48: Insert "Data for the protocol-specified improvement outcome was subsequently reported online by the PACE study authors [manuscript reference 19]"

Line 72-4: Text insertion: "This small difference was reported as statistically significant, but [we conjecture] that it would very likely fail to do so using an intention-to-treat approach. There are a number of possible approaches consistent with the intention-to-treat principle. It would help the reader to clarify the particular approach to which the authors refer.

Line 77: Replace "finally" with "later".

Line 77: Text insertion: "there was no evidence that any yielded [statistically] significant treatment effects at 52 weeks".

Line 84-5: Provide numbers and/or incidence rates per group. Note that the number of serious adverse events in GET group was similar to the APT group [4, Table 4].

Line 86: Provide number and percentage of respondents in each group.

Line 135: Should read "[6, see Supplementary materials, Table C]"

Line 136: Please provide a brief description of how the relevant figures for the long-term follow up analysis excluding those receiving 10 or more sessions of CBT or GET post-trial were derived from Table C of the supplementary materials of [5].

Line 167: Provide number and percentage of study subjects receiving/not receiving a substantial dose of CBT/GET in each group.

Line 185: Insert "after controlling for multiple testing" at end of this sentence.

Line 188-9: Remove one of the final two sentences in this paragraph for redundancy.

Line 204-5: Clarify that this choice has subsequently been defended by the original study authors, e.g. in [3].
Line 206-7: Suggest splitting this sentence as follows: "Turning now to recovery rates, the definition of recovery used in published reports was changed substantially from that in the trial protocol. This made recovery much easier to achieve".

Line 218: Insert "We suggest that" at the beginning of this sentence.

Line 218: Replace "more" with "additional".

Lines 218-9: Perhaps summarise comments as objection to use of term "recovery" for this outcome. Perhaps the authors would classify it as a more stringent definition of improvement?

Line 319: Clarify that these changes were made prior to the examination of outcome data [4]

Line 357-8: I would replace "are likely" with "have the potential"

Figures 1 and 2: I think the data in these figures would be better presented in tables or as boxplots (Figure 1 only) with details provided on the number of subjects per group. The linear trend shown is potentially misleading to the reader. If figures are retained, the same symbol should be used for each group across figures.

Figure 2: Please verify that the means and confidence intervals presented in this figure are correct.

Typos:

Line 88: remove "he" before "the"

Line 89: missing "no" before "significant group differences"?

Line 263: replace "a" with "at"

References:


Are the methods appropriate and well described?  
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?  
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?  
If not, please explain in your comments to the authors.

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