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: 1 Date: 03 Nov 2017

Reviewer: Finbarr Leacy

Reviewer's report:

Major comments:

1. Line 71-2, footnote 2: Please provide a detailed description of the re-analysis presented by the original study authors in [1]. Please highlight that it corroborates your analysis of the composite improvement outcome as appropriate throughout the manuscript.

2. Line 193-4: Text insertion: "to examine the effect of original treatment allocation on long-term outcomes [in this subgroup]"

3. Line 196-7: I am not convinced that Figure 1 is relevant to your analysis and should be omitted.

4. Lines 256-8: The strength of evidence provided by the analysis of long-term outcomes is overstated throughout the manuscript. The presented analysis investigates the effect of original treatment allocation on long-term outcomes among the subgroup of patients not receiving any CBT or GET therapy post-52 weeks. While this is potentially an improvement on the original analysis presented in [2], these results should be interpreted with caution due to potential bias induced by missing data and conditioning on a post-randomisation variable i.e. subsequent treatment at 52 weeks. The relationship between subsequent treatment at 52 weeks and long-term outcomes could be confounded by other factors.

The most appropriate analysis would account for time-dependent confounding and treatment using a causal inference method such as marginal structural models - however this is likely beyond the scope of this article and the data available to the authors.
The authors should present an intention to treat analysis relating the effect of original treatment allocation on long-term outcomes among all randomised patients, clearly specifying how missing values are handled.

5. Figure 2 should be omitted as it is potentially misleading. A table presenting the long-term outcome data for all participants and according to subsequent post-trial treatment would be preferable as this would better reflect the analysis actually conducted. This should include the number of participants with observed data in each group.

Minor comments:

Line 113: Text insertion "but given the high and uneven dropout [for these outcome measures], this result should be treated with caution"

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.

Unable to assess

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

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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