Author's response to reviews

Title: Cost-effectiveness analysis of supported self-management compared with treatment as usual in CFS/ME patients in primary care.

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Author's response to reviews:

Dear Editor,

Please find attached a revised manuscript which, we hope, addresses the reviewers' and editors' concerns. Our responses to the particular questions raised by reviewer 1 are presented below.

a) The authors have tested differences between groups using the "non-parametric k-sample test of differences in medians" (page 9 of the manuscript) which appears to be described as a "non-parametric test that the 3 groups have the same median" on page 12 of the web appendix. Unfortunately I am unfamiliar with the technique, though the authors also test using ANOVA adjusting health expenditure in the 6 months prior to the trial as an alternative and reach very similar conclusions.

Response: We have amended the description of the test and trust that this is more easily understood

1. The "Cost GBP" label on Fig 1 is still unclear and reading upwards/backwards. The authors claim in their reply to my previous comments that this has been replaced, however on the copy of the manuscript that I have seen the error is still there. I wonder if they authors have redrawn the figure but used the old graph file
by mistake.

Response: We are unsure what has happened here. The legend on the y-axis on the version we have seems correct and easily readable. Perhaps it is an error on conversion to pdf? We will check again once the pdf is created.

2. Pages 7 and 10 both describe missing data as having been dealt with using multiple imputation which would imply to a reader that multiple imputation was used for all missing data. However on page 1 of the web appendix missingness described as “Type 1” (where the patient attended the relevant interview but their responses were not recorded for one or more of the questions) was imputed using univariate methods. While the techniques described do seem appropriate and the detailed description of the techniques used is best left in the appendix, the phrasing in the main text is presently misleading. Perhaps words to the effect that the majority of missing data were imputed using multiple imputation with univariate techniques used for some of the less common cases would resolve this. A reference to the web appendix would then allow the reader to investigate further should they wish. The latter sections of the paper could then simply state the results as being under “imputation” rather than “multiple imputation”.

Response: The reviewer is absolutely correct. The majority of missing data were dealt with using multiple imputation, but some missing items were imputed using univariate measures. This has been amended in the text.

3. Page 5 of the Web appendix describes the regression for total costs as using baseline EQ-5D as a covariate. Page 9 of the main document describes ANOVA testing using health expenditure in the 6 months prior to the trial as a baseline covariate in the analysis for patient and family costs. I would be surprised if the authors hadn’t meant baseline costs rather than baseline EQ-5D in the total costs regression. Please disregard this comment if baseline NHS costs were unavailable and Baseline EQ-5D was used as a surrogate, though if this is the case please consider clarifying the matter as a discretionary recommendation.

Response: Adjustment for baseline covariates is recommended to improve precision in the estimate of the difference in costs. While, in principle, a whole range of covariates could be included, the reality is that these are likely to be highly correlated and we therefore chose to use baseline health status as a covariate which was consistent with the adjustment made for QALYs.

We have expanded on our description of choice of covariates in the web appendix.
4. Page 12 of the Web appendix details costs observed in the trial which were borne by the patients and their families. This shows medians, lower quartile (LQ) and upper quartile (UQ) alongside a column marked “Pr(x=0)” which carries the label “fraction of participants who reported zero for this variable”. The only interpretation I can think of for this is that it is the percentage of patients who did not incur an expense in this category. However this would not match up with the medians/quartiles. For example Help from informal carer (hours) for PR has a Pr(x=0) of 0.61 (presumably 61%) and a median (lower Quartile, upper Quartile) of 22(0, 155). If over 50% of the patients in the group had zero utilisation the median would also have to be zero. Similar anomalies occur in almost all entries on the table. Presumably I have misinterpreted this data, but im afraid I cant seem to work out any alternative interpretation. This would suggest that it is either too unclear or incorrectly calculated.

Response: Again, the reviewer is absolutely correct. We presented 1-Pr(x=0) rather than Pr(x=0) as we claimed. We have now corrected this and the anomalies have therefore been resolved.

5. Page 13 refers to figures A3 and A4, however A4 (a CEAC for the complete case sensitivity analysis) does not appear to be included in the paper or the appendix. Has it been left off by mistake?

Response. The Ceac is presented in the main paper and figures A3/A4 should have been omitted from the web appendix. These have now been removed. The CEACs for the multiply imputed datasets and the complete case analysis are almost identical and there is little need to present both.

- Discretionary Revisions

1. In my last comments I noted that the treatment as usual (TAU) arm of the trial was sometimes marked as usual care on graphs. The Authors claim in their reply to the comments that this has been amended, however at least on fig 1 it is still marked as usual care. Though as I note above I suspect the old version of figure 1 has been uploaded in error.

Response: As with comment 1 above, we are unsure what has happened here but trust that a readable version with the correct legends will be uploaded this time.

2. Page 12 of the web appendix which details the costs falling on patients and their families is quite large and cumbersome as medians, lower quartiles and
upper quartiles are presented in their own boxes. Consider offering them in the form median(lower quartile, upper quartile), in the above example of Help from informal carer (hours) for PR this was reduced to 22(0, 155) which would comfortably fit into a single column for each of the arms of the trial which would hopefully condense the table without loss of detail.

Response: Agreed, and we have made this change

3. Similarly Table 3 is also fairly cumbersome. I wonder if there is a way to reduce it a little. Although admittedly no obvious method to do this springs to mind without losing some of the detail.
Response: If the editors can suggest a way for us to make the table easier to read without losing detail, we will happily do it!

4. Page 7 of the paper describes QALYs as the product of the health state of each individual and the time spent in that state. While this is perfectly true using the word product in the mathematical sense (and any economist would likely recognise the description), the information is only new to non-economists to whom I wonder if it would appear unclear. Perhaps adding “calculated as” to the start of the sentence would help clarify this.
Response: We have amended text as requested.