Reviewer's report

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

**Version:** 2  **Date:** 29 November 2012

**Reviewer:** Andrew Stoddart

**Reviewer's report:**

I have assessed the health economic aspects of the paper. The paper has benefited from its revision and most of my previous concerns have been appropriately addressed. The few which remain are largely cosmetic or discretionary. The paper remains generally well written and the interpretation of the results seem reasonable.

I have assessed the econometric and imputation techniques described in the paper to the best of my abilities. Where I have been able to do so I am happy they are appropriate, however there remains one area which I feel under qualified to comment on. That is the appropriateness of the methodology used in the secondary outcomes relating to costs borne by the patient and family. 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.

I hope my comments are found to be otherwise useful.

- Major Compulsory Revisions

  • All my previous concerns in this section have now been addressed.

- Minor Essential Revisions

  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.

  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”.

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.

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 I’m afraid I can’t seem to work out any alternative interpretation. This would suggest that it is either too unclear or incorrectly calculated.

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?

- 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.

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.

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.

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.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests