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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Version: 2 Date: 26 October 2012

Author's response to reviews: see over
Dear Editor,

Re: manuscript number 4074614627891623 - Cost-effectiveness analysis of supported self-management compared with treatment as usual in CFS/ME patients in primary care.

Please accept our resubmission of this research article. We have addressed the reviewers’ comments as outlined below:

Reviewer’s report
Title: Cost-effectiveness analysis of supported self-management compared with treatment as usual in CFS/ME patients in primary care.
Version: 1 Date: 11 September 2012
Reviewer: Andrew Stoddart
Reviewer’s report:
Main comments:
I have assessed the Health Economic aspects of the paper. The paper is generally well written and the interpretation of the results seem generally reasonable. It is difficult to comment on the adequacy of the methodology as some elements could use clarification. However I expect that in most cases once these have been made clearer the techniques applied will be revealed to have been suitable. I hope my comments are found to be useful.

Discretionary Revisions
1. Labelling of Usual Care on Graphs does not match the term treatment as usual (TAU) in text. While it is obvious that usual care and treatment as usual are the same thing (and it is unlikely this would confuse a reader) the paper would benefit from consistency.

Reply: All references to this group in the text, figures and tables now read treatment as usual

2. The reader is offered very short descriptions of the interventions being assessed which do not include specific details of the interventions key cost elements, instead they are referred to the clinical paper. While a full description is clearly unnecessary given that it has been previously published, the brief addition of specific details regarding the number of and length of visits in each intervention would aid the readers understanding of how the intervention costs are constituted without needing to look elsewhere.

Reply: A brief description of resource use associated with delivery of intervention has now been added to the decision problem paragraph on p5, and the resource use section on p6.

3. Table 2 is cumbersome and difficult to read due to large number of boxes, while it provides an excellent source of information, consider formatting the table
more clearly. Perhaps even just putting brackets around SDs to differentiate from the means would help.

Reply: We agree that there is a large amount of data presented and have improved presentation by bracketing the Standard deviations.

Minor Essential Revisions
1 Several items on Table 1 are not referenced to a source. While these are likely to be the NHS Reference costs 2007/8, this is not technically specified. Items include: Cost per elective bed day, Cadiac Intensive Care Unit, Outpatient, Daycase procedure, A&E and phlebotomy. Additionally Neither the PSSRU unit costs or the Reference costs 2007/8 appear in the references for the paper despite being referenced as sources in Table 1.

Reply: References have been added to all sources

2 The “Cost GBP” label on Fig 1 is unclear/backwards (ie reads up rather than down and letters partially merge making it difficult to read).

Reply: Replaced

Major Compulsory Revisions
1 In general the methodology around the economic impact of CFE/ME on the patient and family is not specified clearly with considerable omissions.
   a) The data collection methodology, though presumably recorded by patient recall like the NHS costs have been, is not stated. The paper only states that “data was collected” though in the discussion a questionnaire is mentioned.

Reply: All data were collected using patient questionnaires, and this has been clarified in the text.

b) Any price weights applied these items are not specified. These could easily be added to the bottom of Table 1. How lost Income has been calculated in particular is unclear. What theoretical basis was used (presumably a human capital approach) and did this include absenteeism as well as presenteeism? How were these measured and what wage rate was used? Or were patients perhaps asked directly about the cost itself?

Reply: The trial questionnaire collected information on informal care, out of pocket expenditures, time off work, lost earnings and lost leisure time. Lost earnings and private expenditures related to CFS/ME was estimated from these patient estimates as part of the patient questionnaire. The opportunity cost of informal care was costed per hour equivalent to home help. Lost leisure time was not costed. This is now stated in Table 1. While we have not imposed a theoretical basis on productivity losses, as the reviewer correctly identifies this is implicitly based on a human capital approach whereby the value of an individual is assessed through their contribution to output. As these estimates were not included in the cost/QALY estimates and are only
presented for information purposes, we did not wish to lengthen the paper with much detail regarding these costings. More information is provided in the web appendix.

The trial did not collect data directly regarding presenteeism (reduced productivity while at work due to illness). For those who are working, these productivity losses are to some extent captured by the EQ5D and hence form part of the QALY measure.

c) Similarly the discussion around testing non-NHS costs refers to a significant difference in medians of lost leisure time but no units of measurement or quantities lost are stated. The results in Table 2 include lost earnings which may incorporate leisure time if leisure has been priced at the same rate of lost work but if so this does not disentangle the leisure time specifically.

While I expect that standard/accepted techniques will have been applied here, and I realise that increasing detail too much could dominate the text, there is presently insufficient information given in the paper to allow the analysis approach used to be assessed. Also any limitations of any techniques used (such as a human capital approach) are not discussed.

Reply: See discussion above. In general, we do not feel that this is the right place for a discussion of the rights/wrongs of the human capital approach. We have asked patients for estimates of lost work/leisure time but these estimates have not been included in the primary analysis. This is in line with current UK guidance and with common practice.

2 Cost data for weeks 20 – 44 were not recorded. To compensate for this the authors have imputed costs for this period based on trends in the observed periods. The fact that this happened is not explained in the methods section but rather in the results. The methods sections ought really to specify the time points/periods at which data was collected, that the mid-period was imputed and ideally how this was done. Any assumptions made in this imputation are not specified. This time period unfortunately directly follows the intervention period and it is during this time (judging by the EQ-5D and main clinical results) it is believed that the benefits of the PR intervention diminish. However the trajectory of this deterioration is presumably unknown. Similarly with EQ-5D having only been measured at weeks 0, 20 and 70, QALYs estimated from the EQ-5D results has an implicit assumption of a straight line depreciation between weeks 20 and 70 (see fig 2). While this may be a reasonable approximation since the results appear to converge at week 70 it may also be impossible to tell. Consideration over how assumptions used in imputing costs for this time period or applying a straight line to EQ-5D results between weeks 20 and 70 are not discussed. Given the small absolute magnitudes of the effect sizes it is possible that differences in this period from the imputed values or peaks/troughs in EQ-5D scores could have an effect on the results. That said the absence of evidence of long term benefit of PR over usual care (TAU) may limit the appeal of PR even if a short lived QALY gain were reported and it would be reasonable to consider such a point against this limitation if it is discussed.
Reply: The imputation of costs during weeks 20-44 is now described in more
detail in the “missing values” section.
Also additional point made in the discussion section.
The web appendix gives more detail on the methods, results and validation of
the imputation procedures

3 A minor revision which is related to the above issue (and I apologise if this
seems petty), it is technically unclear what has been done for the complete case
sensitivity analysis for costs during the unrecorded period weeks 20 to 44 (which
reports not to have used imputation). This is due to the unfortunate need to use
the word “impute” for both filling in the missing time period and filling in missing
follow up data. While I expect that costs at weeks 20 to 44 have been imputed for
all patients but only the results from patients with no missing week 20 or 70
questionnaires have been included in the complete case analysis, Table 4`s
reference to the complete case analysis as being “without imputation” may be
misinterpreted by some readers. The paper would benefit from clarifying this
point.
Reply: This is now clarified in Table 4.

4 The authors use a base year of 2008/09 however many of their price weights in
Table 1 reference PSSRU 2010 (which uses a base year of 2009/10) and do not
claim to have made any inflation adjustment. As far as I can see they may have
missreferenced the source or simply made a small typographical error on the
table both of which could be easily amended. But there is a risk that they may
have used different PSSRU reports for different variables cases and not always
inflated/deflated to the 2008/9 base year.
Reply: This is a mis-reference. It should be PSSRU 2009 and has now been
amended. All refs in tables are now hyperlinked to Endnote references also.
To give two quick examples:
a) GP home visits are priced at £117 per visit and referenced to PSSRU 2010.
The figure in the 2010 edition of PSSRU is £120 (page 167) where as the figure
in the 2009 PSSRU is infact £117 (page 121). Several other items referenced to
PSSRU 2010 appear to also be the 2009 edition (District Nurse, practice nurse,
Nurse specialist and physiotherapist at least) and if so can easily be fixed by
correcting the source referenced.
b) General Practitioner (presumably surgery) visits are priced at £36 per visit,
which is the PSSRU 2010 price (page 167) rather than £35 in PSSRU 2009
(page 121). It is likely this may simply be a typographical error on the value on
the table but if not then they have used the wrong base year on this item.
Admittedly a £1 difference on a single item shouldn’t change the results a great
deal but it may be indicative that other items have not been adjusted to the
correct base year. Particularly in light of the absence of quoted sources for some
items (see above).
Before the validity of the price weights can be assessed meaningfully the table
needs to be checked for errors and amended appropriately with each item
checked to ensure the correct base year has been used.
Reply: See response above, the cost of the GP visit has been amended
Reviewer's report
Title: Cost-effectiveness analysis of supported self-management compared with treatment as usual in CFS/ME patients in primary care.
Version: 1 Date: 1 October 2012
Reviewer: Claire Hulme
Reviewer's report:
Overall a well presented paper that will be of interest to the reader.
Discretionary revisions:
1. The background section was a little confused particularly the explanation of the basis of pragmatic rehabilitation. I suggest rewording.
Reply: This section has been simplified

2. Whilst the clinical study is reported elsewhere more explanation/description of TAU would have been useful
Reply: A description of TAU has been added to the text.

3. Table 1 should be in the methods section.
Reply: I would generally put table 1 in a results section, but am happy to move it.

Editorial comments
In addition we have addressed the following editorial team’s comments as follows:

"Thank you for submitting this manuscript to BMC Family Practice. As you will see the reviewers were generally favourable towards this manuscript though they raise a number of points which should be addressed in a revised version of the manuscript. I note that the methods refer to a semi-parametric bootstrap analysis and one of the reviewers was rather unclear about what was involved. A reference or some description of the difference from non-parametric bootstrapping would be helpful."


Editorial requests:
Please include a full, explicit patient consent statement.
Reply: Included in the first section of the method.

Please move the role of funder statement to the Competing Interest section.
Reply: This has been done.

Please move the funding statement to Acknowledgments section.
Reply: This has been done.

Please move the Contributions section to Authors’ Contributions section.
Reply: This has been done.

Yours sincerely
Richard Morriss
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University of Nottingham