Reviewer's report

Title: Cognitive behavioural Internet therapy -- CBIT trial. A randomized controlled trial testing the efficacy of a web-based cognitive behavioural intervention for adult patients with chronic fatigue syndrome: study protocol.

Version: 3  Date: 20 May 2015

Reviewer: Kim Goldsmith

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Review of the Protocol of the CBIT trial, Janse et al, for BMC Neurology

General

I would like to congratulate the authors on a well written paper and a clear study design.

It would be good for the authors to refer to SPIRIT protocol checklist/publication to check all the necessary information has been included, and then refer to the SPIRIT publication in this paper. http://www.spirit-statement.org/spirit-statement/

Review questions

1. Will the study design adequately test the hypothesis?
   a) The paper would benefit from a more explicit statement of the hypotheses.
   b) The six-month follow-up time point is immediately post-treatment. It would be helpful to have information after a longer follow-up treatment period to see if effects persist. I assume the design is as such because the control is a wait list condition – perhaps the authors could elaborate on why they are not following the patients up for longer, or whether they have plans to do so, and why they chose wait list instead of a more active control, such as relaxation.
   c) Also, is there any scope for taking extra measurements earlier in the follow-up period, perhaps for the purposes of explanatory analysis?
   d) I was unsure why the trial didn’t include a face-to-face CBT arm, which is presumably still the gold standard. The authors describe plans for another study in future in the discussion that would include face-to-face CBT. Perhaps earlier in the paper, the background for example, the authors could explain why they have not included a face-to-face CBT arm in the trial.
   e) I was somewhat surprised there were no exclusions based on participants having other psychiatric illnesses, unless this is somehow addressed in the process of referral for CFS?
   f) Could I clarify that the people providing the interviews described in the
Intervention section of the Methods were the people that had helped with designing the web intervention used in the trial and that web-based CBT is not otherwise available to patients outside the trial?

g) Could the authors clarify the reasons for categorising patients as low and high active? Is this simply to provide the correct therapy? Or is it expected to impact on outcomes? If it is the latter, perhaps the authors can explain why they did not stratify randomisation for activity level.

2. Are sufficient details provided to allow replication of the work or comparison with related analyses: if not, what is missing?

The paper makes a very clear and detailed explanation of the study.

I have a few queries/suggestions:

a) Some clarification of exactly when questionnaire measurements are taken would be helpful. These seem to be taken during the two intake appointments as well as at other times. I would suggest adding these appointments to the diagram in Figure 1 so the figure includes all instances where measurements are taken, with the diagram then clearly showing when T0 and T1 are taken.

b) I found the randomisation and unblinding section of the Methods a bit unclear. Why couldn’t all randomisations be done at the second intake? Why would the administrative assistant be on the phone with the patient? Why are the randomisations done in the presence of the patients, and were there precautions taken to ensure the patient didn’t see the randomisation result on the screen? Are the test assistants different from the administrative assistants? And are the test assistants blinded?

c) How will patients be defined as low/high active, what are the decision rules?

d) What will be done where actometer data are missing?

e) How will CBT homework be measured? Presumably there is some online method that can be applied to both web CBT arms and email contact is not the only way this will be assessed, as it will be very different in the two web CBT arms.

f) Adherence, dropout, and treatment integrity section: what will constitute adherence?

3. Is the planned statistical analysis appropriate?

The analysis is appropriate in general. I have a few comments/queries:

a) I am not sure multiple imputation is necessary if predictors of missing data were added to the model and data missing at random was assumed, however, the imputation approach is reasonable.

b) The number of imputations should be equal to the % of missing data.
c) Have the authors considered using earlier screening results in the models as well as baseline? This might help to increase precision further.

d) The clinical improvement outcome will require a logistic model.

e) Change the sentence starting on line 325 in the Sample Size Calculation section to say, ‘Assuming a drop-out rate of 15 percent we will have to include 80 patients in each group to have 95% power to detect the expected difference….’

f) Could the authors please justify why they did not adjust the sample size calculation for clustering by therapists?

g) Defining patients as to activity level begs the question of whether the authors believe this is a potential moderator of treatment. If so, a description of this analysis should be included.

h) Secondary Outcome Measures section Line 272 – is there a reference for the cutoff at 35 on the CIS?

4. Is the writing acceptable?

The paper is very well written. There are some corrections/suggestions under ‘Minor issues not for publication’ below.

Minor issues not for publication
Line 48 – rearrange, i.e. ‘also named ME () by patient groups’
Line 73 – for instead of in?
Line 84 – as effective as face-to-face CBT in that population (?)
Line 260 – weighted instead of weighed

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare that I have no competing interests