Author's response to reviews

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.

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Author's response to reviews: see over
Dear Professor Ying Lou,

We would like to thank you and the two reviewers for their comments and the opportunity to resubmit a revised version of our manuscript. We think the manuscript has substantially improved and hope it will be accepted for publication in BMC Neurology.

In this cover letter we have detailed the modifications that we have made to address the problems identified by the reviewers. We address them point-by-point and highlighted the changes made in the text of the manuscript.

In response to the remarks of reviewer 1:

1. 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/

We now refer to the spirit protocol and have checked that all the necessary information has been included.

We adapted the manuscript as follows:

Interventions 11b:

“...when practical problems with the program occur or when communication between therapist and patient is not sufficient to resolve a specific problem via email or by chatting, telephone contact will be offered to the patient.” This is added to the subsection ‘Intervention’.

Interventions 11c:

“The therapist will aim to write the emails in such a way that it motivates patients to follow the instructions of the intervention.” This is added to the subsection ‘Training and supervision’.

Interventions 11d:

“...were requested not to follow other treatments for fatigue during participation in the study.” This is added to the subsection ‘Ethical approval’.

Data collection methods 18b:
“After randomization patients will receive a letter with the second assessment date and the face-to-face session with their therapist for evaluation of the web-based intervention or start of treatment for the wait list controls. Patients will receive reminders when questionnaires are not completed within one week. When patients do not want an evaluation session, the researcher will contact the patient with the request to complete the assessment as previously agreed. When a patient does not want to complete the full assessment, he or she will be requested to only fill in the questionnaires that assess the primary outcome measure.” This is added to the subsection ‘Assessments’.

Data monitoring 21a:

“We did not use a data monitoring committee for this study. All data will be monitored by a data-manager of the department who is not part of the research team.” This is added to the subsection ‘Assessments’.

Confidentiality 27:

“All participants have a study number in the data file. The file connecting study numbers with identifying personal data is separately stored and protected with a password that is only known to the principal investigator.” It is added to the subsection ‘Assessments’.

Confidentiality 29:

“All authors will have access to the final dataset.” This text is added to the subsection ‘Assessments’.

Dissemination policy 31a:

“Patients will receive written information about the study results when the paper reporting on the study has been published.” It is added to the subsection ‘Ethical approval’.

Informed consent materials 32:
A translated informed consent will be attached as an appendix at submission.

2. The paper would benefit from a more explicit statement of the hypotheses.

We agree and have added the following hypotheses:

1) “Fatigue severity will be significantly lower at second assessment following web-based CBT compared to the wait list control group.

2) Patients who receive web-based CBT will report significantly less disabilities and psychological distress and significantly more often show clinical significant improvement in fatigue compared to the wait list control group.

3) Patients who received protocol driven feedback web-based CBT will report a significantly larger decrease in fatigue severity, level of disability, psychological distress and report more often a clinical significant improvement than patients who received web-based CBT with feedback on demand.”

We’ve added these hypotheses in the ‘Background section’.

3) 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.

Thank you for your feedback. There are two reasons why there is no controlled follow-up period. The first reason is that patients on the waiting list, have to wait for the start of regular CBT. Due to a limited treatment capacity the waiting period is 6 months. Having them to wait longer is unethical as treatment capacity for regular CBT is such that treatment can commence at 6 months. The medical-ethical board in the Netherlands will not give permission for a longer waiting period. The second reason is that the proposed study will be continued as a randomized noninferiority trial in which web-based CBT, followed by face to face CBT if patients did not profit from the internet intervention, will be compared to care as usual, i.e. face to face CBT after the waiting period (Dutch trial register NTR4809). This is the second reason why a longer follow-up period is not feasible. We do agree that the lack of a follow-up assessment is a limitation of our study and now mention this as a limitation in the discussion:

“This study has some potential limitations. We have no controlled follow-up assessment in our study. We will not be able to determine if the expected positive effects of the web-based intervention are sustained over a longer period. A longer
follow-up period is not possible as our study will be continued as a randomized noninferiority trial comparing the two forms of web-based CBT followed by face to face CBT if patients have not profited from the internet intervention (stepped care) with care as usual, i.e. face to face CBT following the waiting list. This randomized noninferiority trial is registered in the Netherlands trial register (NTR4809).”

In reaction to your remark on adding an active control arm we added a potential limitation in the discussion section:

“Second potential limitation is that the treatment effects cannot be controlled for non-specific factors of the interventions. As this study will be continued as a randomized controlled noninferiority trial, an active control was not possible. Previous research has shown that CBT is significantly more effective than other active interventions, like guided support groups and specialist medical care (Prins et al, 2001 and White et al, 2011).”

We mentioned references were already mentioned elsewhere in the paper.

4) Also, is there any scope for taking extra measurements earlier in the follow-up period, perhaps for the purposes of explanatory analysis?

Thanks for sharing your thoughts about the possibility of taking extra measurements earlier in the follow-up period. Unfortunately, we will not include such extra measurements mainly due to financial and logistics constraints. We will however analyse the use of the web-based intervention, e.g. how many modules have been followed or how many times a patient logged in.

5) 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.

The proposed study will be continued as a randomized noninferiority trial in which web-based CBT, followed by face-to-face CBT if patients did not profit from the internet intervention will be compared to care as usual, i.e. face-to-face CBT after the waiting period (Dutch trial register NTR4809).

We addressed this issue in the discussion section of the paper.

6) 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?

We apologize for omitting the relevant information concerning exclusions based on the presence of psychiatric illnesses that exclude the diagnosis of CFS.

During the first intake session the Mini International Neuropsychiatric Interview (MINI) will be completed to assess the presence of psychiatric disorders. We discuss this in the subsection ‘Study population’ under the section of Methods/Design.

“We will assess the presence of psychiatric disorders using the MINI and clinical assessment and exclude patients who do not meet the inclusion criteria of the CDC with respect to current psychiatric disorders and/or having a medical history with psychiatric disorders.”

7) 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?

The patients providing the interviews were indeed the people that had helped with designing the web intervention before the trial started. The web-based CBT is not otherwise available to patients outside the trial. We address to your remark in the subsection ‘Intervention’ of the section Method/Design and added:

“Three out of these seven patients were interviewed. Excerpts of these interviews were reported in this trial paper. After the pilot study, the intervention will only be available to patients participating in the study and allocated to one of the treatment arms.”

8) Could the authors clarify the reasons for categorizing 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 randomization for activity level.

Categorizing patients as low or relatively active is used for tailoring therapy. There is a specific protocol for low active and relative active patients. Following Stulemeijer (2005), who found similar effects of CBT for low active patients and relative active, we expect the same outcome for low or relatively active patients. Therefore we did not stratify randomization for activity level.

To the subsection “Low active versus relative active.” of the section Methods/Design we added:
“Following Stulemeijer (2005) we do not expect different treatment outcomes for low or relatively active patients.”

We added the following reference:


9) 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:

10) 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.

We have added the figure adapted from the SPIRIT example template. It is added at the end of the paper and is referred to at the ‘Outcomes’ subsection of the section Method/Design.

Figure 2 - Schedule of enrolment, interventions, and assessments.

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<thead>
<tr>
<th>STUDY PERIOD</th>
<th>TIMEPOINT**</th>
<th>Enrolment</th>
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<td><strong>ENROLMENT:</strong></td>
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<td>Informed consent</td>
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<td>Allocation</td>
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<td><strong>INTERVENTIONS:</strong></td>
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<td>CBIT: protocol driven feedback</td>
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<td>CBIT: feedback on demand</td>
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<td>Wait list control group</td>
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11) I found the randomization and unblinding section of the Methods a bit unclear. Why couldn’t all randomizations be done at the second intake?

Following the rules of the medical ethical committee we give patients one week to consider if they want to participate in the trial.

In the ‘Randomization and blinding’ subsection of the Method/Design section we added:

“Patients are contacted one week later to ask them if they want to participate in the study. An administrative assistant will call the patient and will perform randomization during this phone call. If patients do not need time to think about their decision and decide to participate, randomization will take place immediately at the second intake session.”

12) Why would the administrative assistant be on the phone with the patient?

The administrative assistant is on the phone with the patient if the randomization was not performed during the second intake session. See also previous answer to remark 11.

13) Why are the randomizations done in the presence of the patients, and were there precautions taken to ensure the patient didn’t see the randomization result on the screen?

Randomizations are done in presence of the patient so they can see the outcome is not influenced by the therapist or assistants. Patients are able to see the outcome of the randomization. They can read on the screen ’1) Internet therapy’ or ’2) Internet therapy’ or ’wait list’.

In the ‘Randomization and blinding’ subsection of the Method/Design section we added:
“After randomization, therapists and patients will be able to read the randomization result on the screen i.e. ‘1) Internet therapy’ or ‘2) Internet therapy’ or ‘wait list’.”

14) Are the test assistants different from the administrative assistants?

The test assistants can be the same person as the administrative assistant.

15) And are the test assistants blinded?

The test assistants nor the administrative assistant will be blind to treatment allocation.

We elaborated further in reaction to your remarks:

“Therapists and test assistants are not blinded with respect to condition. This will most probably not introduce a bias as there is no contact between test assistants and patients following randomization. The test-assistant sends a link via email to the patient, patients will fill in the questionnaires at home.”

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

The decision rules are explained in detail in the paper of van der Werf (2000). We explained this in the subsection ‘Low active versus relative active’ of the section Method/Design and added:

“The individuals’ activity patterns will be based on the 12 daily physical activity scores (van der Werf, Prins, Vercoulen, van der Meer, & Bleijenberg, 2000). Two physical activity patterns can be discerned. The average daily physical activity scores of low active patients stay below the general mean physical activity of CFS patients in at least 11 of 12 days. Relative active patients score at least 2 of 12 days above the mean physical activity score of CFS patients.”

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

When patients will have missing actometer data at baseline, they will be asked to wear the actometer again. When for some reason the actometer data will be still missing, the activity pattern is determined by the therapist on the basis of a structured interview (Scheeres et al., 2008).

We added at the end of the ‘Low active versus relative active’ subsection:
“In case of missing actometer data at baseline, therapists will determine the activity pattern by using a structured interview (Scheeres et al., 2009).”

We added the reference:


18) 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.

The CBT homework will be measured on several ways. We can evaluate:

1) The number of logins.
2) The mean time of logins.
3) The number of fully opened modules i.e. meaning all texts of the particular module have been opened.
4) The number of completed reflection assignments at the end of each treatment module.
5) The distribution of emails and/ or number of opened modules and/ or chat sessions per month.

We will assess and report these variables.

We added to the section “Adherence, drop-out and treatment integrity”:

“We will assess how patients have used the web-based CBT by registration of .... 4) the number of sent emails and chat sessions. These variables will be reported.”

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

It’s hard to define what will constitute adherence to the web-based treatment as little is known about what the patient does with the information offered. We have however formulated criteria to determine if a patient adheres to the treatment regime.

In the subsection ‘Adherence, dropout, and treatment integrity’ we added:

“We assume that a patient adheres to the web-based CBT with protocol driven feedback if:
- He or she at least fortnightly emailed to the therapist, and
- has opened at least each module of the web-based intervention once.

We assume that a patient adheres to the web-based CBT with feedback on demand if:
- They have opened at least each module of the web-based intervention once.”

20) 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.

21) The number of imputations should be equal to the % of missing data.

In response to the comment of the reviewer we changed the number of imputations in:

“Multiple imputation using fully conditional specification will be used to handle missing observations. The number of imputations will be at least equal to the percentage of missing data of the outcome measure. The assumption is made that data are missing at random (Von Hippel, 2011).”

We added the following reference:


22) Have the authors considered using earlier screening results in the models as well as baseline? This might help to increase precision further.

We considered using screening results in the models. As the reliability of the primary outcome measure is high not much is gained by using screening results, the ANCOVA analysis with baseline measure added as covariate most probably will lead to an optimization of power (Breukelen, 2006). We therefore decided not to use results of screening in our models.

We added the following reference in response to this remark in the subsection ‘Statistical analysis’ of the Methods/Design:

Van Breukelen, G. J. ANCOVA versus change from baseline: more power in randomized studies, more bias in nonrandomized studies [corrected]. Journal of Clinical Epidemiology 2006, 59(9): 920-925.

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

Our apologies for this omission. We corrected this omission in the ‘Statistical analysis’ description and will use a chi-square test to determine if the proportion of patients with a clinical improvement outcome significantly differ between treatment arm and wait list condition.

We added in the statistical analysis subsection:
“We will use a chi-square test to determine if the proportion of patients with a clinical improvement outcome significantly differ between treatment arm and wait list condition.”

24) 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….’

We thank the reviewer for this suggestion to improve readability. We changed it as suggested.

“Assuming a drop-out rate of 15 percent we will have to include 80 patients in each group to have 95 percent power to detect the expected difference of 6.7 points on the CIS fatigue between each of the CBT formats and the wait list condition.”

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

We did not adjust the sample size calculation for clustering by therapists for a number of reasons. 1) It should be noted that therapists are not nested within one treatment condition, all therapist will deliver two modes of interventions. 2) Also note that it is not quite clear what the impact on the sample size calculation would be. The estimate for the (residual) standard deviation of the outcome that we use in the power calculation is obtained from trials that neglected a (possible) therapist effect. 3) Research so far has shown that there is no therapist effect in delivering CBT for CFS (Cella et al., 2011; Heins et al, 2013). For this we decided not to adjust the sample size for clustering by therapist.

References:


26) 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.

Thank you for this point of review. We refer to our answer to question 1g. Based on the RCT of Stulemeijer et al. (2005), we do not expect a difference in outcome. Determining the activity level will only be used to determine which interventions have to be delivered.

Reference:

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

The cut-off score of 35 has frequently been used as a criterion to indicate clinically relevant fatigue in clinical studies (Knoop et al, 2007; Wiborg et al, 2014). This is two standard deviations above the mean of healthy controls (Vercoulen, Alberts, & Bleijenberg, 1999).

We added the following reference in the ‘Primary outcome measure’ paragraph:


The other two references were already part of the reference list.

28) Line 48 – rearrange, i.e. ‘also named ME () by patient groups’

We changed this into “i.e. often also named ME (myalgic encephalomyelitis/encephalopathy) by patient groups”

29) Line 73 – for instead of in?

We changed this in ‘for’.

30) Line 84 – as effective as face-to-face CBT in that population (?)

We changed this in ‘in adolescent CFS patients’.


We changed this in ‘weighted’.

**In response to the remarks of reviewer 2:**

1. When does the recruitment begin and has the recruitment already started now?

   The recruitment has started in March 2013.

2. At several places in the methods section the authors write in the past tense, as if the study has finished already. That should be corrected.

   We have changed the past tense to the future tense at several places in the methods section.
3. The paper says that test assistants will do all assessments. but it is not clear whether they will be blinded for the condition to which the patients are assigned or not.

In response to your remark we added information in the ‘Randomization and blinding’ subsection of the Method/Design section we added:

“Therapists and test assistants are not blinded with respect to condition. This will most probably not introduce a bias as there is no contact between test assistants and patients following randomization. The test-assistant sends a link via email to the patient, patients will fill in the questionnaires at home.”

4. Why are administrative assistants not blinded for the conditions?

They will have minimum contact with a patient, see our response to your previous remark and changes in the manuscript for further elaboration on this remark. The only contact they will have with a patient is mentioning the randomization outcome: internet therapy or wait list control trial. The administrative assistant was not informed about the differences between both web-based CBT formats. We address to this remark in our response to remark number three.

5. The analyses are well described and adequate. However, I don't understand why only five imputations will be done. Why not 25 or even 100?

Thank you for your thought about the missing data. We changed the number of imputations in:

“Multiple imputation using fully conditional specification will be used to handle missing observations. The number of imputations will be at least equal to the percentage of missing data of the outcome measure. The assumption is made that data are missing at random (Von Hippel, 2011).”

We added a reference for this rule:


6. The power calculation is OK, except that I think a drop-out rate of 15% is rather low. Is that based on earlier trials?

We assume that the best prediction for the drop-out rate is the drop-out rate of previous research testing the efficacy of guided self-instruction, what can be seen as the precursor of CBIT. The first trial evaluating the effect of the guided self-instruction the drop-out rated was about 5% (Knoop et al., 2008) and around 12% in the second study (Tummers et al., 2012). Based on this numbers we used 15% drop-out as a conservative estimate.
We added in the sample size calculation both references which were already part of the reference list:

“Assuming a drop-out rate of 15 percent, based on previous trials testing the guided self-instruction (Knoop et al., 2008; Tummers et al., 2012), we will...”

We hope that we have adequately responded to the remarks of the reviewers,

On behalf of my co-authors,

Anthonie Janse