Author’s response to reviews

Title: Investigating the effectiveness and cost-effectiveness of FITNET-NHS (Fatigue In Teenagers on the interNET in the NHS) compared to Activity Management to treat paediatric Chronic Fatigue Syndrome (CFS)/Myalgic Encephalomyelitis (ME): Protocol for a randomized controlled trial

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Investigating the effectiveness and cost-effectiveness of FITNET-NHS (Fatigue In Teenagers on the interNET in the NHS) compared to Activity Management to treat paediatric Chronic Fatigue Syndrome (CFS)/Myalgic Encephalomyelitis (ME): study protocol for a randomized controlled trial

We are delighted to have received such positive comments from your reviewers and to be offered publication in your journal subject to minor revisions. We have addressed each comment by the two reviewers as outlined below, and submit a revised manuscript with tracked changes for clarity. We feel that the manuscript has been strengthened by the amendments we have made in response to the comments we received.

We very much look forward to publication in your journal.

With very best wishes,

Emma Anderson

On behalf of all the authors.

Reviewer 1

The rationale for not including a usual care group. The pathway for such a group is provided in Figure 1, and the Dutch study upon which this intervention was developed included a usual care group that allowed "individual or group-based rehabilitation programmes, cognitive behavioural therapy face-to-face, or graded exercise treatment, or both, by a physical therapist." Now, the inclusion of a usual care group may complicate the study instead of a straightforward comparison between online CBT and activity management using video calls, but it needs to be acknowledged somewhere that not including a usual care group could also limit the value of the study as well.
Thank you for this thoughtful comment. The funders insisted that those in the control arm received a NICE recommended treatment. The clinical service currently offers Activity Management delivered by Skype (and one face to face assessment), so the control arm in FITNET-NHS does deliver “usual care” provided by a specialist service. For most children in the UK, “usual care” is no treatment. We accept that having Activity Management treatment as a comparison may reduce the comparative efficacy, but given that it is possible for some children with CFS/ME to access treatment long distance using this model, we feel this is the most appropriate test for the NHS.

- We agree that the manuscript is strengthened by clarifying this and have amended the text in the sections detailed below.

Please see:

- ‘Background’, paragraph 2
- ‘Methods’, paragraph 1
- ‘Methods’: ‘Setting and trial population’, paragraph 1
- ‘Methods’: ‘Interventions’; paragraph 1
- ‘Strengths and limitations; paragraph 4

By not having a usual care group, the implicit assumption if one treatment is found to be clinically effective will be that online CBT or video calls in activity management will be at least as effective as current care for the study population. This may well turn out to be the case but it needs stated that this is the assumption at this stage.

- The FITNET-NHS Trial is designed to compare FITNET-NHS (delivered as online CBT) with Activity Management which is what patients accessing CFS/ME from a distance would receive. The only difference is not having to travel for the initial assessment as that is delivered via Skype as well as the follow ups (which are delivered via Skype to long distance patients as part of usual care). We have clarified this in the manuscript as above

Further to this it was not really clear upon reading, what usual care involves, until Figure 1.

- Thank you. This is now addressed with the above clarification.

It would be good if the main text could allude to Figure 1 more frequently when describing the intervention, e.g. p8/24 (or 9/30 in the pdf).

- Thank you for this comment. We have amended the text to allude to figure 1 sooner and more clearly.
Also I wondered what the rationale was for comparing a 6 month intervention with a 3 month one? This may be down to how these interventions were designed, but it would be useful to understand whether or not the difference in potential intensity can be considered?

- Thank you for your comment. This is a pragmatic trial comparing two different treatments. We are delivering Activity Management as it is currently offered to those who do not have a local specialist service as a ‘usual care’ treatment, and are comparing it with the FITNET-NHS treatment that was tested (and shown to be effective) in a Dutch trial. There are many differences between the two interventions, of which intensity is one. It is the assessment of overall effectiveness and cost-effectiveness that are the main aims of this trial. The integrated qualitative methods explore participants’ experiences of the two trial treatments which will show what treatment features are important to families. We agree that if differences in effectiveness are found between the treatments, further research will be required to explore mechanisms of effectiveness. We have amended the conclusion to state this.

Please see:

• ‘Discussion’: Final sentence

Also, given there is no video-call CBT or online activity management arm (again may be down to how the interventions were designed originally) it may also be useful to consider how differences in mode of delivery between the arms may influence results?

- As above, this is a pragmatic trial of two treatments to assess overall effectiveness and cost-effectiveness. We are exploring participant experiences of the trial treatments, including mode of delivery, using integrated qualitative methods. We have amended the text on qualitative outcomes within the discussion to show this clearly.

Please see:

• ‘Discussion: Strengths and limitations, paragraph 1

I also wondered about intellectual property for the intervention(s) and whether this needs mentioned?

- Thank you for highlighting this. IP arrangement is complex and is a legal document. We do not believe it will add to the paper and is not a requirement to report, just a requirement not to infringe.

The authors have done well to note the difficulties associated with the EQ-5D-Y in the absence of an existing value set for it. But I did wonder, given the use of the SF-36 physical score as the
primary outcome, why the full SF-36 instrument could not just be used as these values can be converted to utilities. Cost? Proxy considerations? It may be useful to state somewhere.

- Thank you for this suggestion. Our previous qualitative work with teenagers suggest that this is too much of a burden and contributes to the loss of outcome data.

The authors are undertaking secondary analysis on those with co-morbid mood disorders as CBT is said to be less effective among adults with co-morbid depression (p17 -or 18/30 of the pdf - lines 33-36). But care should also be taken in case this is not the case among the study population of interest. So those without co-morbid mood disorders should also be considered, given that they will account for 70% of the study population (as opposite is cited on p5-24 - or 6/30 of the pdf - lines 11-12).

- Our primary outcome is efficacy in children with CFS/ME, most of whom will not have a mood disorder. This trial is powered to enable us to also look at those with a co-morbid mood disorder as a secondary analysis, to address the evidence gap that exists for this important clinical subgroup.

- We state:

“Secondary subgroup analysis will investigate the effectiveness of FITNET-NHS in those with co-morbid mood disorders” in the abstract, and make this clear at many points throughout the manuscript.

We have added a sentence to the discussion to emphasize that we are addressing the evidence gap within this trial.

Please see:

• ‘Strengths and limitations’: paragraph 2

Reviewer 2

1) Abstract: In the method section (line 25, page 4), "the study will assess whether FITNET-NHS is effective". Cost-effectiveness is also one of the major trial's objectives and is mentioned throughout the manuscript but not in the method section in the abstract.

- We stated cost-effectiveness at the end of the methods and analysis section of the abstract. We agree that it should be clear this is one of the major trial objectives and moved this statement earlier to show this more clearly.

Please see:

• Abstract: ‘Methods and analysis’
2) Abstract: In the discussion section, focus is entirely on effectiveness and cost-effectiveness results of the trial. A comment could to be included on the feasibility and acceptability in the internal pilot as prerequisites of a definitive trial before jumping to effectiveness and cost-effectiveness.

- We agree that this should be included. We have added a comment on feasibility and acceptability.

Please see:

• Abstract: ‘Discussion’

3) Methods (Randomisation): The method used to generate the random allocation sequence and the person who will generate the random allocation sequence, the person who will enrol the participant are clearly detailed. However, the reason for not blinding participants and clinical service is not stated until the last paragraphs of the manuscript.

- We state the following within the paragraph on randomisation (methods section): “Because of the nature of the intervention, it is not practical to blind either the participant, family or the clinical service to treatment allocation. GPs will be informed of the allocation.”

- We do not feel any revision is necessary on this point.

4) Methods (Interventions-Activity Management): The interventions section is very detailed and clear. When the word “activity” is mentioned in some instances (e.g. line 9 page 8) it is clearly described as "cognitive activity". Although, there are instances where activity is not described as either disease, cognitive, functional, physical, or overall activity. A description of the type of activity that is being monitored will add more clarity.

- Thank you for this comment. We have amended the manuscript to indicate that ‘activity’ includes cognitive activity (this is an element of the treatment model that is not immediately apparent).

Please see:

• Activity management (comparator), first paragraph

5) (line 34, page 8) Furthermore, it is not clearly stated but rather implied with whom the therapists will discuss the case of each individual by phone. From my understanding this is the primary/secondary care clinician.

- Your understanding is correct, and we have amended this sentence for clarity.

Please see:

• Activity Management (comparator): final paragraph
6) Methods (Sample Size): A sample size calculation is conducted based on the main outcome SF-36-PFS for the full study. However, there is no information about the desirable recruitment (rates) in the internal pilot that would meet the criteria of continuing to a full definitive trial.

- Thank you. We have added a sentence to make it clear that the full trial would only go ahead assuming stop criteria were not met, and we reference the stop criteria (described under ‘outcomes and analyses of the internal pilot study’). The stop criteria were more complicated than just numbers due to the complexity of the trial and taking into account seasonal variation and qualitative data.

Please see:

• Sample size: first paragraph

7) Methods (Outcomes and analyses of the full trial - cost effectiveness of FITNET NHS and Activity Management): Outcome measures and the time intervals are clearly stated in outcome measures section. They are consistent with the literature and cover a extensive range of outcomes for CFS/ME. (Line 21-28 Page 15) It is clearly stated that EQ-5D-Y will be used and that at the time of the analysis EQ-5D-Y valuation tariff will be used if available. From my understanding if it is not available, the value set for adults will be used. For the authors' information, there are other alternative generic measures of Health Related Quality of Life for children/adolescents which have already been validated and valuated in the UK. An example is the CHU-9D.

- Thank you for this helpful information! We have been selective in our choice of questionnaires to minimise respondent burden. We understand from the EQ5D-Y developers that a value set should be available by the end of the FITNET RCT.

8) Table 2: Dummy tables Adherence to trial, and intervention characteristics by group can be added to complement the Patients' characteristics and outcomes dummy table.

- Thank you for this comment. We have added a row on adherence to treatment to table 2. We have also amended the paragraph describing the rating of adherence to treatment for clarity.

Please see:

* Table 2

* Interventions: Treatment adherence

Language corrections:

9) (line 56 page 13) "...full trial if: 1) if the recruitment…" The word "if" should be omitted.

10) Discussion: (line 58 page 16) word "have" should be omitted.
- These two language corrections have been addressed. Thank you for your diligence.

11) Discussion: (line 39 page 16) word "whether" should be omitted.

- The word ‘whether’ is needed in this sentence. We state:

“FITNET-NHS is designed to treat young people with co-morbid mood disorders as well as CFS/ME and this study is powered to test whether the effects of FITNET-NHS differ in this subgroup of young people.”

We do not feel any revision is necessary on this point.

- Additional amendments:

In addition to addressing the reviewer comments, we have clarified the wording in places (e.g. giving the full wording of General Practitioner, before its abbreviation; making consistent use of ‘study’ for the pilot and ‘trial’ for the overall RCT). We have also updated the author and affiliation details, removed a reference that was not needed, and added an acknowledgement of the REDCap database used for data collection.

- Since initially submitting these revisions (in early October), we have had an ethical amendment to increase the number of Activity Management sessions offered within the trial to up to six sessions (one assessment and up to five follow ups). This was approved by the South West -Frenchay Research Ethics Committee on 19 October and HRA on 23 October. We have revised the manuscript accordingly.

Please see

• Interventions: Activity Management (comparator)

• Duration of treatment period

• Figure 1