Reviewer’s report

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

Version: 0 Date: 03 Aug 2017

Reviewer: Dimitrios Tzelis

Reviewer’s report:

Overview:

The manuscript develops the design of a randomised control trial with the purpose of evaluating the effectiveness and cost-effectiveness of FITNET intervention in the NHS. FITNET is a CBT treatment for CFS/ME in young populations that can be provided via internet to individuals who do not have access to local specialist services. As part of the study an internal pilot will be conducted to examine feasibility of recruitment and acceptability of treatment.

General Comments:

Overall the protocol is well written on an interesting topic about a CFS/ME treatment for children, for which there is good evidence of its effectiveness elsewhere (Nijhof et al. 2012). However, it is essential to evaluate the effectiveness and cost-effectiveness within the NHS setting to inform funders' decisions.

The methods used to generate the random allocation sequence and the person (s) who will generate the random allocation sequence, the person (s) who will enrol the participant and also the person (s) who will assign the participants to the interventions in comparison is clearly detailed. Finally, the methodology for the economic analysis is very clearly described, as well as for the sub-group analysis for children with CFS with comorbid conditions.

Without changing any of the research, I believe the article could be improved with some of the following comments or recommendations:

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.

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.
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.

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.

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.

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.

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 valued in the UK. An example is the CHU-9D.

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.

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.

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

Level of interest
Please indicate how interesting you found the manuscript:
An article whose findings are important to those with closely related research interests

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

**Quality of figures**
All images and figures within the manuscript should be genuine i.e. without evidence of manipulation. No specific feature within an image may be enhanced, obscured, moved, removed, or introduced. If you have concerns about the veracity of the figures you should choose the first option below.

**Statistical review**
Is it essential that this manuscript is seen by an expert statistician? If so, please give your reasons in your report.

**Declaration of competing interests**
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?
2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?
3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?
4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?
5. Do you have any other financial competing interests?
6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare I have no competing interests.
I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal