Reviewer's report

Title: Testing non-inferiority of blended versus face-to-face Cognitive Behavioural Therapy for severe fatigue in patients with Multiple Sclerosis and the effectiveness of blended booster sessions aimed at improving long term outcome following both therapies: – study protocol for two observer-blinded randomized clinical trials

Version: 0 Date: 13 Sep 2019

Reviewer: Riaz Qureshi

Reviewer's report:

This protocol describes a two-stage RCT to (Stage 1) test the non-inferiority of a blended cognitive behavioural therapy (MS Fit) with standard face-to-face CBT, as well as (Stage 2) the effectiveness of using internet-based "booster sessions" (MS Stay Fit) as compared with no booster sessions on long term outcomes, among those who complete assessments in the first stage.

Comments General:

* The protocol is well written and the aspects of the trial protocol which are present are well described, however there are many elements which are missing and which require clarification.

Comments (SPIRIT Reporting):

* It seems that descriptions for many SPIRIT items have been omitted that, in our view, are applicable to any randomized controlled trial. One possibility is that what the items refer to were not done in the trial; another is that you may see the description as unnecessary. When an item is truly "not applicable", it is to your advantage to provide a succinct explanation so that the readers understand the rationale for not addressing the item on the SPIRIT checklist in their protocol. Please provide a brief justification if these elements are truly irrelevant to your trial, or if they are relevant (which we think most of them are), please provide succinct descriptions. Additionally, if some is "not applicable" because it was not done, please provide a statement as to why it was not done in the manuscript and SPIRIT checklist. If there are items which have been included but have been left out of the SPIRIT checklist, (some examples provided below), please update the SPIRIT checklist and ensure that all page numbers are correctly specified. Please see the SPIRIT explanation and elaboration guidance for more information on each of the items (Chan, BMJ, 2013; 346: e7586).

* Examples: 2b, 3, 5c, 5d, 11b, 13, 17b, 18b, 19, 20b, 20c, 21a, 21b, 23, 25, 26b, 27, 29-33 i.
  Item 2b - Although the trial is not registered in the WHO Trial Registration Data Set, please provide the items from your current registration or a statement that they can all be found within the protocol. ii. Item 3 - Your protocol version and date are found on page 20. iii. Item 5c - There
is a statement on page 22 that the study sponsor will not have any role in the design, conduct, or writing of the study. Please update your SPIRIT checklist accordingly. iv. Items 5d, 19, 21a, 21b, & 23 - Will there be any oversight of the trial to monitor progress (e.g., check if recruitment is lagging or progressing well, periodically check data quality, ensure training of study staff has been appropriately conducted, especially if new staff are brought on at any center over the duration of the trial)? Are there any plans for how to handle study termination if something unexpected were to occur (e.g., the first stage of the study does not find non-inferiority or finds that it is worse than face-to-face CBT, would the second stage still continue)? If not, please provide a brief statement as to why. There is mention of a trial Steering Committee on Page 12, Line 19. Please provide more information about the composition, roles, and responsibilities of the steering committee. v. Item 13 - Your SPIRIT figure is referenced on Page 13 and should be noted in the checklist as such. vi. Item 18b - The planned follow up is for a year; will there be any efforts made to retain participants over that duration and prevent loss to follow up? vii. Item 20c - Related to the above: if there is loss to follow up, how will missing data be handled in analyses? Will any missing data methods be used? Will any attempts be made to try and reach participants who have missed study follow up visits? viii. Item 25 - If changes need to be made to the protocol, how will these be communicated and to whom? ix. Item 26b - Please include a statement that handling of biological specimens is not applicable to this trial as none will be collected for any outcomes x. Item 27 - What measures are being used to ensure patient data security? E.g., any password protection for databases, or locked drawers for patient completed forms, the use of patient-specific study IDs instead of names to protect identities, etc. How long will patient data be kept and who will have access to it? If any of this information is included in the ethics application and/or the informed consent form, it can be included in the protocol as well. If no measures are being taken, please include a statement in the protocol to that effect.

* Several SPIRIT items are not completely described and require further elaboration. Please see the SPIRIT explanation and elaboration guidance for more information on each of the items to ensure they are fully described (Chan, BMJ, 2013; 346: e7586). Examples: i. Item 12 - Outcomes can be further defined. Please see following comment for clarification. ii. Item 18a - The plans for assessment of outcomes are presented in the Figure 2 and in the summary of outcome measures (page 13, lines 25-34), but do not include any description of plans for assessing data quality. This is related to Item 19 (described in an above comment), but includes any approaches that may be taken to help improve the quality of the data that is being collected (e.g., range checks for data, checks for missing values left off by patients in the forms which they are completing, etc.). If there are no plans for this, please include a statement to that effect. iii. Item 22 - How will adverse events be collected? Systematically (i.e., with a checklist at regular intervals), and/or non-systematically (i.e., with open-ended questions about patient experiences)?

* Please fully define all your outcomes following the framework described in Zarin NEJM 2011;364:852-60 and Saldanha PlosOne 2014;9(10):e109400. Your outcome definition should include these 5 elements: the domain (name of the outcome), specific measurement, metric, method of aggregation, and time point. The current definition for primary outcome includes the domain (fatigue), measure (CIS20r), but is missing the metric (i.e., will the difference at a point in time between groups be assessed, or the difference in the change in score between two groups, etc.), the method of aggregation (e.g., mean, median, proportion, etc.), and the time point (i.e.,
which of the times at which the outcome will be assessed is the primary end point; 39 weeks or 52 weeks). Please also specify the secondary outcomes to the same extent.

**Level of interest**
Please indicate how interesting you found the manuscript:

An article of importance in its field

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Please indicate the quality of language in the manuscript:

Acceptable

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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.

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

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No