Author’s response to reviews

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

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Dear Editor,

Thank you very much for reviewing our paper entitled: 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. We have read the reviewer’s comments and made adjustments in the paper accordingly. We are pleased to hereby re-submit our paper. Below we will elaborate on each specific comment of the reviewer.

Reviewer #1: 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, re-randomized 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): I. 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 Thank you for your comments and explanation. We have added and specified the items in the revised manuscript according to the referred guidelines, and we updated the SPIRIT checklist. In the revised manuscript the following descriptions were added: 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. We have inserted the WHO Trial Registration Data Set as a supplementary Table 1. From this supplementary table as much information as possible was also included in the manuscript. ii. Item 3 - Your protocol version and date are found on page 20. Thank you, we have updated this in the revised SPIRIT Checklist, and adjusted the page number after all corrections. 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. Thank you, we have updated this in the SPIRIT Checklist. 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. With regard to the monitoring of the trial, we have included: “Monitoring This study will be subject to on-site monitoring in accordance with the quality assurance advice of the The Dutch Federation of University Medical Centres regarding research involving human subjects [63]. On-site monitoring will be based on the risk-classification of the study (negligible). The sponsor/investigator will submit a summary of the progress of the trial to the Ethical Committee once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/serious adverse reactions, other problems, and amendments.” (page 20 of the revised manuscript) Also, we added a description of the Trial Steering Committee “The steering committee of the trials consists of the authors of this paper and a member of the Dutch patient organisation MSVN.” Page 26. The roles are explained at the end of the manuscript in “author’s contributions”. v. Item 13 - Your SPIRIT figure is referenced on Page 13 and should be noted in the checklist as such. Thank you, we have updated this in the SPIRIT Checklist. 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? We included a section on participant retention: “Participant retention Participants receive the questionnaires online. For optimal retention, participants will be contacted by email or phone by the research assistant, when they have not started the completion of the questionnaires within one week. Randomization is done after
completing all questionnaires at T0 (R1) or T20 (R2), preventing missing data at these important moments. When participants are not willing to complete all measurements at T20, T39 or T52, they are asked to at least fill in the subscale fatigue of the CIS20r, being the primary outcome measure.” (page 17/18) 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? We aim to prevent loss to follow-up as much as possible, and do not plan on imputation of missing data. When participants complete the questionnaires, they are not able to skip any items. We inserted a section on Participant retention and added this description to the paragraph on outcome measures: “Completing the questionnaires online requires filling in every item, which prevents occurrence of missing item values. The research assistant checks for possible missing sleep logs, and, if needed, sends as a reminder additional sleep logs to the patient.” (page 14). viii. Item 25 - If changes need to be made to the protocol, how will these be communicated and to whom? We added information on this in the section on Ethical approval: “Any changes in the protocol will be sent for approval to the Medical Ethical Committee first. After approval, the adjusted protocol will be sent to all primary researchers from the participating centers.” on page 25. 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 We have included this statement: “Biological specimens No biological specimens will be collected in the study.” on page 20. 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. We have inserted a section on Handling and storage of data and documents: “Handling and storage of data and documents Data, other than the questionnaires, are entered in an electronic Case Report File (eCRF), which includes an audit trail. Personal data will be handled confidentially and in a coded way, and comply with the Dutch Personal Data Protection Act. Patient identification will be coded for all study procedures. Only the project leader and primary researcher have access to the codes and participant data. Codes and participant data will be stored in password-protected files. After finishing the study, the key to the code will be safeguarded by the coordinating investigator. Data will be stored by the Department of Rehabilitation Medicine of the Amsterdam University Medical Centers for 15 years following completion of the project. Therapist secrecy and confidentiality will be maintained at all times. Patient correspondence by e-mails will be encrypted and securely stored to guarantee privacy and confidentiality. An email-account of the university hospital will be used for correspondence by emails. Participant information will not be disclosed to third parties. Only the Trial Steering Committee will have access to the full dataset.” on page 19,20. II. 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. We have adjusted the description of the primary and secondary outcomes according to the SPIRIT guidelines and named several time points more explicit in the descriptions of the outcome measures and other determinants (pages 14-17). In addition, we added a supplementary table 2, in which all 5 elements are described per outcome measure. 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. We have inserted information on this in the section on Outcomes and Participant retention, as mentioned above in our response on item 12 and 18b. 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)? We added information on the collection of serious adverse events: “Serious adverse events Any spontaneously by patient or therapist reported adverse events will be recorded. CBT, both face-to-face and blended, are expected to be safe treatment methods. However, all serious adverse events (SAEs) will be reported according to the Dutch Act on Medical Research Involving Human Subjects. An SAE is defined as any untoward medical occurrence or effect that is lethal and/or life threatening, requires hospitalisation or prolongation of existing inpatients’ hospitalization, results in persistent or significant disability or incapacity. SAEs will be reported to the researcher by the therapists, during by-weekly supervision or by email. All SAEs need to be timely reported to the Medical Ethics Review Committee. When adverse events occur appropriate diagnostic procedures and medical treatment will be undertaken as needed. The Ethical Committee has granted dispensation for insurance for damage to research participants through injury or death caused by the study, as participation in this study is without risks. “ on page 18. III. 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. We have adjusted the description of the primary and secondary outcomes according to the SPIRIT guidelines and named several time points more explicit in the descriptions of the outcome measures and other determinants (pages 14-17). In addition, we added a supplementary table 2, in which all 5 elements are described per outcome measure. IV. In addition to your comments, we added paragraphs on consent on publication and availability of data on page 25,26: Item 31a: “Consent for publication The results of this study will be submitted for publication as scientific articles in peer-reviewed, open access journals. The results will also be presented at national and international conferences for clinicians, researchers and patients. Publication is not restricted to the outcome of the study, all results (positive and negative) will be incorporated in the paper. Item 29: Availability of data and material Any request to share the data of these RCT’s will be considered by the Trial Steering Committee, and will need to be approved by the ethical committee of the Amsterdam University Medical Centers, location VU medical center, before granted.” We also added a paragraph on Participant withdrawal on page 18: Item 18b: “Participant withdrawal Patients can leave the study at any time for any reason if they wish to do so without any consequences. Nevertheless, these patients are requested to fill in a final CIS20r fatigue. The researcher can withdraw a patient from the study in case of incorrect
enrolment of the participant. Withdrawing from the study, does not necessarily mean the patient has to stop treatment. The treating physician, or the treating psychologist can decide to withdraw a patient from the study for urgent (medical) reasons. These reasons will be documented.” And a paragraph on Modification of allocated intervention on page 13: Item 11b: “Modification of allocated intervention Reasons for discontinuing the allocated intervention can be new health problems or life events hindering patients to continue the treatment, or patient’s decision to withdraw from the treatment. After eight months a small adjustment was made in the introduction page of MS Fit, after receiving feedback of two patients who found the description not applicable to them, demotivating them to continue treatment. These sentences were adjusted, and an example was added, in order to clarify the purpose of the blended CBT..” As a supplement to this letter we added an overview of all figures and tables. We sincerely hope that you will find our adjustments sufficiently clarifying and that our revised manuscript is suitable for publication in Trials.

Yours sincerely,

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