Reviewer's report

**Title:** Neuropsychological Management of Multiple Sclerosis: Evaluation of a supervised and customized cognitive rehabilitation program for self-used at home (SEPIA): protocol for a randomized controlled trial

**Version:** 1  **Date:** 14 Jul 2019

**Reviewer:** Angie Logan

**Reviewer's report:**

Thank you for addressing my previous comments, and those of Reviewer 2.

Lines 57 & 58 currently reads "As there is evidence based that computerized program may be a practice option for CR and that quality of life is poorly evaluated in CR studies..." Is quality of life "poorly evaluated in CR studies" or is there a lack of studies evaluating CR" reword to "Evidence suggests that computerized programs may be a practise option for CR for people with MS, but there is a paucity of studies evaluating quality of life", or the last part of the sentence could be "... but lack of rigour in evaluating quality of life has been identified in previous CR studies".

Line 88: currently reads "difficulties in meeting the demands of their jobs lead active people to be more ..." consider rewording to "difficulties in meeting the demands of their jobs resulting in people being dismissed, reclassified or unemployed"

Line 94: "In this sense ..." delete and rewrite ". Cognitive rehabilitation (CR) may represent .." Delete "ideal" in this sentence.

Line 96 "pharmacological ones" replace with "pharmacological interventions"

Line 97, add "s" to "option" as it should be "options"
They offer self-paced, individualized training...

They allow, for patients who be concerned, a feasible, simple and friendly activity that require ...

Avoid starting sentences as per line 103 and 107 with a reference e.g. "Stuifbergen et al. conducted an at-home computer-based CR trial in order to help MS patients to achieve the highest level of cognitive functioning and functional independence. They showed that the intervention group outperformed the control group on all measures including a better personal efficiency, more frequent use of compensatory strategies and improved performance in neuropsychological tests [3]. In addition, Messinis et al. reported improved verbal and visuospatial episodic memory, information processing speed and executive functioning after an intervention of 20 individualized one-hour sessions over a 10-weeks period using RehaCom® 110 software in relapsing-remitting (RR) MS patients with mild to moderate cognitive disorders ...

Lines 111 and 112 " Few studies included assessment of activities of daily living as secondary outcomes, among other criteria, with promising results". It would be helpful to the reader to state this was a systematic review as "few studies", then seeing only one reference looks odd. Consider rewording "A systematic review identified a paucity of studies including activities of daily living as secondary outcomes ...

Lines 167-176, remove the full stop.period at the end of each line. There should only be on on the last line which is line 177. Same applies to lines 180-192.

Line 198: "motivate exclusion of the trial." replace motivate with "result in"
Lines 198-199: "However, outcome data will be collected on those patients and included in the intention-to-treat analysis" do you mean outcome data that has ALREADY been collected? Currently this reads as though you will continue to collect data after the person has been excluded.

Line 261: "... patients will be informed about the aim, the benefits, the constraints and ..." too many "the". Write to "patients will be informed about the aim, benefits, constraints and risks of the trial"

Line 265 All assessments and screening will take place in "the MS Expert Centre" will you be providing transport or reimbursing money for travel?

Lines 270-273 remove ; from the end of each line

Section "Screening assessment" Starting line 266: I think you need to make it clear to the reader that it is a two stage eligibility assessment. The way I have interpreted from reading is they are screened for eligibility, then if eligible they have a battery of assessments, then they are deemed eligible or ineligible based on the scores of those assessments. Is that right?

Line 284: ensure consistent use of participant and patient. You have used "patient" here but previously used "participant". Once they have consented they are a participant.

Lines 291-292, please state when "(alternate forms when appropriate)" will be used and why.

Lines 300-307, again please remove ; from the end of each line

Lines 309-310 Ensure consistency of abbreviations. You have stated in full and then abbreviation in bracket for 246-247 "Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS)", but provided this again here. You can just use BICAMS on line 309 and do this for all your abbreviations.
Line 314 "Intervention" refers to the experimental treatment. Consider using a different title such as "group allocation" or something else. Then have two sections, 1) intervention (which is the CR) and 2) Control (active control).

Line 319: "will run during 8 consecutive weeks" change to "will run for eight consecutive weeks". Numbers 1-9 should always be written in full.

Lines 322-324. I note the authors explanation in the reply to reviewers comments about "active control". "The word "active" refers to the fact that it was not ethically possible to randomize patients in this group without any psychological care as some patients may be disappointed by the result of the randomization". What is the usual care for cognitive rehabilitation? Have you considered a different trial design where the participants who are initially in the control group and receive nothing, but only have the tests, are then offered the intervention at the end of the intervention period?

Lines 338-339: " Psychologist can also rely on an automatic level progression system that ensures participants start with an easy configuration and then automatically progress to their own "challenge zone" where they will be pushed to develop strategies" please revise to improve grammar, e.g. "The computer programme has an automatic level progression ensuring participants start with a level that the participant deems easy. This will automatically progress to a "challenge zone" where level of difficulty will be increased to challenge participants."

Line 341 "pushed" this is a colloquial term. Do you mean participants will be "encouraged"?

Lines 342-343 this needs a reference and consider rewriting to improve grammar.

Line 346: "be provided by the referent neuropsychologist" revise to improve grammar. If this is related to the scores from the battery of tests, it would be helpful to state this.
Line 349: "Patients will performed autonomously, on their own speed, in the absence of the psychologist". Needs revising to improve grammar. Autonomously suggests on their own, so consider revising.

Lines 353-355 "Importantly, content discussion will be the same as in the active control group to avoid any treatment differences. Finally, feedbacks about their program's progress will be provided" Both these need revising to improve grammar. Delete "Importantly". Start with "Content discussion will be the same in both groups to ensure standardisation" Participants will receive feedback about their progress with the CR program".

Line 357: "will be held one week" should this be "once a week"?

Line 361 "They will also completed" should there be a "d" on the end of "completd"? Doesn't make sense currently.

Lines 368-369: "Adding a long-term follow-up in our trial design will allow us to detect the eventual maintenance of benefits over time in patient's daily life". This needs a reference, but how are you going to account for disease progression in primary progressive and relapses in relapsing remitting MS?

Lines 374-377: " We hypothesized an average increase of 3 points in the MUSIQOL scores at short term follow-up for the active control group (a low effect size, equal to about 0.2) and an average increase of 11 points for the experimental group (0.7 effect size), leading to a 8-points difference between the 2 groups". What are you basing your hypothesis on? The reference you mention in the sentence previous to this? Any data from your pilot study that you can reference here?

Lines 377-380 " Taking a bilateral alpha error of 5% and a power of 80%, a minimal sample size of 18 patients per group is needed to compare the mean scores of the 2 groups at short-term follow-up, adjusting for the baseline scores. To account for potential drop-outs, 20 patients will be included in each group". You need references for these.
Lines 392-393 "Yet, as patients are waiting for therapeutic intervention, we must reckon with most appropriate approaches in our usual healthcare" please write as it does not make sense. Please avoid the word "reckon", this is not appropriate academic terminology.


Line 398: "In this context, we designed an innovative computer-assisted CR intervention at home with a ..." Revise to "In this context we have designed an innovative home-based computer-assisted CR intervention ..." Additionally, this sentence would be better linked with the previous paragraph.

Lines 399-401 once you have move the sentence before this, it is not well placed here. "The choice of this primary outcome was motivated by the paucity of existing CR trials about QoL and the need to provide psychological wellbeing to people with MS.". Consider where else this should go.

Line 404: "the main interest of our trial is to consider" this should be your "aim" not your "main interest".

Lines 405-406. You often use "empty words" e.g. "In that way ..." "rather ...". Try to avoid this. "In that way, we rather adopt a holistic approach in which patient's feelings regarding his/her own care will be stressed" This sentence needs revising.

Line 407: This relates to my point above "We also choose to consider CR ..." you should be providing a rationale for your design and methodology, the word "choose" is a lay term, but you need to be using academic terminology in a clear and readable way.
Lines 408-411 "In our trial, exercises were selected according their relevance in MS as well as their level difficulty. They also provide immediate feedback, so patients can adapt gradually and create/develop strategies increasing both QoL and cognitive functioning." These sentences read as though the trial has been completed. This needs revising to make it clear the trial is going to be conducted in the future.

Line 413" Remove "In fact .."

Line 415: Replace "On the contrary" with "Conversely ...

Lines 417-418: "Feasibility and acceptability of a home-based computer-assisted training program was previously demonstrated in one randomized trial. This needs a reference. This sentence could be reworded to emphasis the lack of studies and provide a stronger rationale for your trial.

Lines 418-419: "A main outcome aimed to systematically examine ..." According to your reference this is an exploratory systematic review, not a comprehensive systematic review or meta-analysis. Revise to "An exploratory systematic review explored the feasibility of home-based computer-assisted training and examined the perceptions of people with MS regarding home-based computer programs for cognitive rehabilitation”.

Line 432: "Results of this trial will provide added methodological data to the existing field of CR studies ..." Revise to "Results of this trial will contribute to the limited body of literature for CR in people with MS" ... or similar.

Lines 439-442: "The trial will concern only RR- and SP- MS patients and our results may not be formally replicated to primary progressive MS even if this form of the disease shares the same pathophysiology and had similar cognitive impact than SP MS". This is not a discussion point, but it could be if you expand it. This sentence needs revising. Do you mean "generalisable" as opposed to "may not be formally replicated to PP MS"? The way it currently reads does not support your rationale for including both people with PP and SP MS.
Line 443: "Based on the expected results of this trial, we anticipate to make this CR program more available ..." This needs revising. You have not conducted the trial, what are you basing your expectations on?

General comments, if you have written an abbreviation in the manuscript, ensure you use this consistently. Quality of life is sometimes written in full and sometimes QoL.

Your title is: Neuropsychological Management of Multiple Sclerosis: Evaluation of the added value of a supervised and customized cognitive rehabilitation program for self-used at home (SEPIA): protocol for a randomized controlled trial, however, it is not clear how they are defining or evaluating the "added value"

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