Author’s response to reviews

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

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DETAILED REPLY TO COMMENTS OF REVIEWER 1

Second revision

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".

These lines have been modified according to the reviewer recommendation
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"

This has been done

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

This has been done

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

This has been done

Line 97, add "s" to "option" as it should be "options"

This has been done

Line 98: "They offer a self-paced, individualized training..." remove the "a" to improve the grammar "They offer self-pace, individualized training ..."

This has been done

Line 101: "They allow, for patients who be concerned, a feasible, simple and friendly activity that require ..." revise as the grammar makes it difficult to read. Additionally, this whole sentence needs a reference. The "for patients who be concerned" should ideally be deleted. I would find a reference that reports computer-assisted cognitive rehabilitation is feasible, simple and friendly, and one that has undertaken an economic analysis to justify your statement of reducing financial support.
As recommended, we deleted “for patients who be concerned”. For the second comment the reviewer had already discuss this point in the first revision. We think there is no doubt in the literature, and from our own experience, about the feasibility of computer-assisted cognitive rehabilitation. After that, one can discuss the best adjectives to better qualify the fact that, really, patients join with a great interest this kind of program. We put again general references on this topic. The statement of reducing financial support is supported, in France, by the fact that cognitive rehabilitation by a health professional is either limited or for psychologist not reimbursed by the health insurance system. As to our knowledge there is no reference on this question we decide to delete this part of the sentence.

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 ...". The reader will appreciate your stating what the outcomes were and discussing this and adding a reference at the end.

We apologize to disagree with the reviewer comment. The outcome is clearly explained regarding the reference of Stuifbergen et al, and can be easily understood from the results of Messinis et al. We do not see what could be the added value, of not to start the sentence with the name of an author except if there are special editorial rules we are not aware.

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 od d. Consider rewording "A systematic review identified a paucity of studies including activities of daily living as secondary outcomes ..."

The sentence has been changed according to the reviewer recommendation.
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.

It has been done

Line 198: "motivate exclusion of the trial." replace motivate with "result in"

It has been done

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.

All subjects will be followed until the end of the study, even those excluded from the trial. Actually, as discussed by Lachin (Lachin JM. Statistical considerations in the intent-to-treat principle. Control Clin Trials. 2000;21(3):167-89), we should have used the expression “withdrawal from assigned treatment” instead of “exclusion from the trial”. As stated in the ICH Guidance on Statistical Principles for Clinical Trials (ICH E9 Expert Working Group. Statistical Principles for Clinical Trials: ICH Harmonized Tripartite Guideline. Statistics in Medicine 1999; 18:1905–1942) and further discussed by Lachin (Lachin JM. Statistical considerations in the intent-to-treat principle. Control Clin Trials. 2000;21(3):167-89) : “The intention-to-treat principle implies that the primary analysis should include all randomized subjects. Compliance with this principle would necessitate complete follow-up of all randomized subjects for study outcomes.” This should be done “irrespective of whether the patient is still receiving or complying with the assigned treatment.”

To be more explicit, we replaced “… will result in exclusion of the trial.” by “… will result in withdrawal of assigned treatment.”

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"

This has been changed according to the reviewer recommendation.
All assessments and screening will take place in "the MS Expert Centre" will you be providing transport or reimbursing money for travel?

The answer is YES. We provide travel reimbursement for all assessments to patients included in the trial.

It has been done.

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?

This is the correct interpretation. To clarify, the second sentence of the paragraph was modified.

Ensure consistent use of participant and patient. You have used "patient" here but previously used "participant". Once they have consented they are a participant.

We replaced patient by participant in the sentence.

Concerning neuropsychological testing alternate forms will be used to reduce risk of practice effects during short-term and long-term assessments. This information has been added in the manuscript.

It has been done.
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.
This has been done.

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).
Title and sub-titles of the paragraph have been modified

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.
This has been done

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?

We apologize but we think that this comment is outside of the purpose of this review. We agree that one have been considered another design, but it would be another trial..., another manuscript.. etc..
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."

Sentence has been revised according to the reviewer recommendation

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

No. The reviewer has well understood the meaning, i.e. it was a progression to a challenge zone with an increased level of difficulty

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

Again, this pilot study was not published as indicated line 130-133. Grammar of the sentence has been revised.

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.

Pre-programmed exercises were set independently of the scores from the screening battery of tests

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.

Grammar has been revised
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".

This sentence has been corrected as suggested

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

This has been corrected

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

This typing error has been corrected

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?

We cannot give a reference regarding a working hypothesis. Considering the second comment we will not include primary progressive MS patients in this trial. We understand that relapses may changed the results of this long-term assessment. Accordingly, this analysis will concern only patients without relapses or progression for secondary-progressive MS patients.

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?
Results from the previous research were only used to estimate the standard deviation of the MUSIQOL scores and the correlation coefficient between scores. Concerning the average increase in the MUSIQOL scores, a zero-point increase could have been hypothesized in the control group but we preferred to allow for a weak effect (based on the concept of “effect size” defined in Cohen, J. (1988). Statistical Power Analysis for the Behavioral Sciences (2nd ed.). Hillsdale, NJ: Lawrence Erlbaum Associates, Publishers) in order to not overestimate the expected difference between the 2 groups. For the experimental group, we hoped for a medium effect (above 0.5 but below 0.8) of the cognitive rehabilitation program. We chose the minimum effect size that was in accordance with the expected duration and planned budget of the study (0.7).

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.

We have added a reference for the sample size formula used in our study. Concerning the drop-outs, figures were based on a 10% drop-out rate, very frequently used in practice and in accordance with the rates observed in the studies supervised by the Clinical Research Unit of our University Hospital.


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.

The sentence has been corrected.


We apologize for this omission. The reference has been corrected.
In this context, we designed an innovative computer-assisted CR intervention at home with a ...  

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.

Unfortunately, moving this sentence seems to us very difficult and we did not find another place in the discussion section to put it. In addition, we are not convinced that moving this sentence would really improve this part of the manuscript. We have therefore chosen not to do that.

"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.

The sentence has been modified in order to be readable.
In our trial, exercises were selected according to 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.

This has been revised

Line 413: Remove "In fact .."

It has been done.

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

It has been done.

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 emphasize 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”.

These two comments are linked. In fact, the two sentences concern the same study (so the same reference added now at the end of the first sentence). It is not an exploratory systematic review but a preliminary report, about some methodological aspects of a randomized single-blind trial published later (reference 42 of the manuscript). We agree that the word “systematically” in the second sentence is confusing as it is more “specifically”. Accordingly, these two sentences were revised
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.

The sentence has been revised as suggested

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.

Changes in the first revised version was a request of reviewer 2. So, we do not want to suppress this point from the discussion section. However, we revised the sentence as suggested.

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?

The sentence has been revised

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.

This has been done

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"

We agree with this comment. Then, we suppressed “added value” from the title.