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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Author’s response to reviews:

Reply to comments of reviewer one:

General feedback

Lots of grammatical errors, which at times makes it difficult to read. Needs more justification in some areas.

We understand this comment and made a lot of effort for improving grammar before submitting revision.

Replace "complaint" to "impairment" so it reads cognitive impairment and not cognitive complaint (see comments for Line 40)

We applied the reviewer recommendation everywhere it was appropriate in the manuscript.

You are doing a RCT so use the word "trial" throughout and not "study"

We fully applied this recommendation.
Line by line comments

Line 35: "In this context, we are interested on the efficacy [...]" should be "interested in the efficacy". Is this the primary objective? If yes, this needs to be made clear.

We have clarified this part of the abstract and modified line 40 of the Methods section accordingly.

Line 40: do people with MS "complain" about their cognition? Consider alternative "who have cognitive impairment" and then add how that is defined, e.g. what severity, because not all people with MS acknowledge or realise they have cognitive impairment.

As suggested “Who complained about their cognition” was replaced with “who have confirmed cognitive impairment”. Cognitive complaint was initially raised as some patients may be screened regarding either spontaneous complaint about their cognition or previously known cognitive impairment. Whatever to be included and randomized cognitive impairment need to be confirmed in the patient at the screening visit. We agree that in the abstract it is clearer to keep only the main criteria.

Line 41: "Patients from experimental group will benefit of the CR program and a psychological support at home during eight weeks”. Consider revising as grammatically incorrect. Additionally, the word "benefit" should be changes as this suggests the trial has taken place and results have suggested patients benefit.

As suggested "Patients from experimental group will benefit of the CR program and a psychological support at home during eight weeks" was replaced with "Patients randomized in the experimental group will perform a home-based CR program with a psychological support during eight weeks."

Line 45: The Training sessions are described as "fun short exercises". Who determined they were fun? This needs to be referenced when addressing this in the main text.

As this adjective was a quite confusing in the abstract, so we decide to delete it. However, before launching this RCT, we made a pilot study on ten patients where we can confirm the feasibility, simplicity and friendly aspects of the exercises. This point has been addressed in the main text.

Line 46: what is the justification for an "active control group"?

We may understand that the term “active control group“ may be a little bit confusing. However, “active” means that it was not ethically possible to randomize patient in the control group without any psychological care. This is because we include a simple psychological support to control non-specific elements of the intervention leading to the term “active” control group that seems to us appropriate in this context.
These terms have been revised and replaced by various issues related to MS such as everyday cognitive-related difficulties or management of emotions.

We agree with this comment. Accordingly, we have modified the beginning of the discussion section of the abstract.

This part of the abstract was also modified regarding the reviewer’s comment.

We agree with the reviewer’s comment that the word “young” is inappropriate in this sentence. Then it has been suppressed.

As pointed out "As well, as current done, assessments does not allow to capture [...]" was replaced with “In addition, current cognitive assessments do not capture real-world [...]” as the original sentence is clunky and grammatical incorrect.

We agree with the reviewer’s comment as rehabilitative approaches may be different depending of health professional. So, we rephrase the first sentence of this paragraph.
Line 103: "They allow an engaging and fun activity" has this been evidenced? This is a
generalisation and potentially some people may not find it fun and engaging.

and

Line 104: "significantly reducing the costs of rehabilitation". What costs? You need to provide
examples of the economic impact.

We agree that the first part of the sentence suggest a generalization that may not be true in a real-
world clinical setting and that the second part may be a shortcut to suggest potential indirect
reduced cost related to rehabilitation care by health professional. Accordingly, we have largely
modified this paragraph.

Line 107: "the control one" should be "the control group".

This has been corrected as suggested.

109-112. You have listed assessments of cognition, e.g. executive functioning but what about
functional ability in activities of daily living?

We added a sentence regarding this criterion.

Line 117-118: "The need for better outcomes measures transparency and related ecological
validity is also warranted" revise grammar

Grammar and the sentence were revised.

Line 119-120: "have used different approaches. Broadly speaking, those who aim at increasing
cognitive performance and those who rather adopt a holistic approach, intending at improving
quality of" revise to "have used two main approaches: those aimed at increasing cognitive
performance (include a reference here) and those that adopt a holistic approach (include a
reference here), aiming to improve quality"

As recommended "Have used different approaches. Broadly speaking, those who aim at
increasing cognitive performance and those who rather adopt a holistic approach, intending at
improving quality of life" was replaced with "have used two main approaches: those aimed at
increasing cognitive performance (reference included) and those that adopt a holistic approach
(reference included), aiming to improve quality of life". We added the requested references.

Line 125: Change "Most of them only aimed" to "Most studies aimed to improve"

"Most of them only aimed to" was replaced with "Most studies aimed to."
Line 126-127: "However, we know that such assessments are [...]" change to "However, these assessments are lacking ecological sensitivity and potential improvements"

As suggested "However, we know that such assessments are lacking ecological sensitivity and potential improvements includes [...] » was replaced with "However, these assessments are lacking ecological sensitivity and potential improvements include [...]".

Line 129: "On theses bases" revise as grammatically incorrect

"On theses bases" was replaced by “According to this overview…”

Line 130: change "at-home program" to "home-based program"

We applied this change.

Paragraph starting on Line 129 is a weak justification for qualitative methodology. This needs expanding to justify why qualitative methodology is needed and what it will add to the existing body of literature.

This paragraph was revised according to reviewer’s comment.

Line 132: change the word complain to impairment throughout the manuscript

This has been done.

Line 132-134 You need to state that these are secondary outcome measures. You also need to justify or explain why you are using these secondary outcome measures.

These secondary outcomes were explained in detail in one large paragraph in the Outcome measurements section. Therefore, it seems to us not relevant to repeat that in the background part of the manuscript. But we added a sentence about the interest of these outcome measures.

Line 149: "Orally and written detailed information [...]" replace with "Verbal and written information". Also need to provide how the verbal information will be standardised. Will you be using a script?

As suggested "Orally and written detailed information about the ongoing study will be provided by investigators" was replaced with "Verbal and written detailed information about the ongoing study will be provided to the patient in a standardized way. For that we use a specific informed consent form that has been validated by the Ethics committee.”

Line 163: "Definite" to be replaced with "Confirmed" to read "Confirmed diagnosis of MS"

"Definite diagnosis of MS" was replaced with "Confirmed diagnosis of MS."

Line 164: Currently states RR and secondary progressive. Should this be or, or and/or?
A patient may have a RR form or a SP form.

Then “Relapsing-remitting (RR) and secondary progressive (SP) phenotypes of the disease” was replaced with “Relapsing-remitting (RR) or secondary progressive (SP) phenotypes of the disease.”

Line 165: Replace with "Be male or female aged between 18-65 years"
This has been done.

Line 169: replace complaint with impairment throughout
In order to clarify the inclusion criteria list, this line has been deleted.

Line 194: "Patients will be removed from the study with no specific procedure". This needs revising as you need a procedure for what you will do if participants get randomised in error, e.g. they don't meet the criteria.

We agree that this sentence is inappropriate due to a wrong copy-paste from a previous version in the submitted version. This sentence is now deleted from this section.

Line 210: references are needed at the end of the sentence "consistency, reliability, reproducibility and acceptability"
References have been added.

Line 229: Is the MCQ-30 self-report or clinician administered? For all outcome measures are they self-completed or will an assessor be asking the questions and the participant reporting?

MCQ-30 is a self-report questionnaire. However, at the time while the patient is filling in the questionnaire, the psychologist is disponible to help him (her) for any question. We now added this point in the section.

Line 251: "evaluated during these 3 assessments" change to "at all three time points"
We applied this change as suggested.

Line 260: "After consent acceptance […]" change to "After patients have provided informed written consent"
We applied this change as suggested.

Line 279: Need to expand this sentence and state that participants and clinicians are not blinded and why blinding is not possible. Will assessors be blinded?
The sentence is now expanded to clarify who is blinding or not and why.
In the intervention section which starts on Line 307, need to add in that the duration of the intervention period is 8 weeks as currently this is not clear. Again, justification as to why you are using an active control is required.

Time schedule regarding intervention period was clarified. Justification for “active control group” is now added to the corresponding section.

Given that participants have cognitive impairment and may have problems with problem solving and attention, how much support are they getting with the program?

In fact, we get an initial experience on ten MS patients with cognitive impairment during an open non controlled pilot study using the same CR home-based program. This pilot study (unpublished) showed that patient get some benefit on their QoL (based on self -perception questionnaire). This result convinced us to develop this trial. This point is now included in the background section.

Line 332: there are quotations marks directly before [29] is this a mistake?

Indeed, it is. Quotations marks were removed.

Paragraph that is line 335-337. No mention of fatigue and how this is accounted for. Given that fatigue is prevalent in people with MS this needs to be mentioned.

This is now explained at the end of the following paragraph.

Line 338: "Then participants will underwent" needs changing to "undergo"

We applied this change as suggested.

Line 340: Why is the intervention period 8 non-consecutive weeks. This needs justifying.

It is a writing mistake. Actually, intervention period last on 8 consecutive weeks.

Line 343: "to promote coping strategies […]" this needs to be more explicit

We modified the sentence in order to explicit this point

Line: 350: "management to attest any improvement" Wil patients who are fatigued going to be given opportunity to break or rest during the assessment session?

Yes absolutely. All assessments will be adapted to each patient situation by our neuropsychologist who are involved in care of MS patients since many years.
Line 352: change underwent to undergo
We applied this change.

Lines 358-360: would be helpful to the reader to refer to the schedule of events table to see what outcome measures you propose.
As suggested, we now refer the reader to the study flow chart and to the table with outcome measurements.

Line 372: What are you basing the potential drop outs of 20 patients on? Need to provide evidence-based justification for this number.

It’s a misunderstanding. It is specified in the same paragraph few lines above that: “a minimal sample size of 18 patients per group is needed to compare the mean scores of the 2 groups.” Then to account for possible drop-out (estimated at 10%, i.e. 2 patients per group) it was planned to include 20 patients per group. We did not modify the sentence.

Line 376: You need to provide a reference for the intention-to-treat analysis and per-protocol analysis and justify why you are using both.

We agree that the sentence regarding ITT and per-protocol analysis was not clear. So, this sentence has been changed and references added in the bibliography.

Line 378: provide a reference for SPSS.
Reference has been added to the bibliography.

Line 382: consider revising to: "To date, pharmacological treatment has not improved"

We revised this line as suggested.

Line 383-384: Yet, as patients are keen for care support” this whole sentence needs revising as does not make sense. Also, what is care support?

Line 384-385: Consider revising to "Such conclusions warrant prioritisation of non-pharmacological, pragmatic, ecological, low-cost alternatives that address difficulties"

Lines 383-385 were revised as suggested.

Line 386-387: Need to justify and reference the statement "computer-assisted CR may bring flexibility, dynamics, objectivity, ecological validity […]

The sentence has been simplified and we added a reference regarding this point.
We applied this change.

The sentence has been revised.

Sentence has been revised.

Sentence was modified according to reviewer’s comment.

Grammar has been revised and the sentence modified in order to better explain the outcomes.

Paragraph starting line 418 to 421 is difficult to understand and grammar is poor. Needs revising. What does "find their best path" mean on line 420? Lin 421 what does "educated patients" mean?

Main text from line 408 to 421 have been largely revised in order to answer all comments of the reviewer.

We applied this change.

Revised as suggested.

Additional information was added to the text.
Line 426: You state you "expect to make this CR program more extensively available", consider revising to "anticipate".

Revised as suggested.

Line 427: "to anyone interested", are you aiming the program at people with MS directly or via clinicians who are working with people with MS in both hospitals and community settings?

If the trial is positive, we planned to share this program with health professional working with people with MS in both hospitals and health networks dedicated to the disease.

Line 429: Sounds like you are focusing just on MS care centres. This may be appropriate for your country but need to consider international relevance as this is not necessarily true in the UK.

We agree that the paragraph regarding these two comments (line 426 to 431) needs to be clarify. We revised these lines in order to better described clinical perspectives related to the trial.

Line 429-431 "Indeed, we must be able to propose rehabilitation to any patient in demand who cannot enter a study because of the strict inclusion-exclusion criteria" needs revising as does not make sense.

We agree with the comment regarding this unsuitable sentence that we decided to delete.

Line 434: need to add in the date the first participant was recruited.

We update the information about trial status.

Comments about the table at the back with the visits and outcome measures on:

Baseline assessment is not clear from the list of visits.

We made an effort to clarify each assessment in the manuscript and figures.

According to the main text, MUSIQoL is used at baseline, after 1 week and 6 months yet is only listed once in the table (line 211).

Detailed neuropsychological assessments at screening, baseline, 1 week and 6 months after CR are now presented in the table.

Weeks and months appear to be used interchangeably with regards to trial timelines. Need to be consistent and choose either weeks or months, not both.

These discrepancies were now corrected using only week timelines.
Reply to comments of reviewer two:

Abstract section:

Why are you going to evaluate QoL 1 week after intervention and not just after the intervention?

Indeed, this is the case within few days. As patients follow home-based cognitive rehabilitation (CR) program 3 times a week they have their last session most of the time on Friday. Then they have to come to the MS expert centre to get their short-term assessment. This appointment is planned before the end of the CR period, but it usually needs 2 or 3 days according to the availability of the patient. This explain why we stated that QoL will be evaluated, more precisely, during the next week of the end of home-based CR.

Main text

Lines 92-95: If traditional neuropsychological evaluation systems detect adequately cognitive disorders but cognitive complaints not, should you include the first one system as the gold standard to select the sample?

We agree with the reviewer’s comment which connect with a similar comment of reviewer one. In fact, as impaired cognitive performance at one test of the BCcogSEP battery is mandatory for selection criteria, neuropsychological evaluation is really the gold standard for inclusion in the trial. Accordingly, we have modified abstract and main text regarding this confusing point.

In general, should you prevent low levels of treatment adherence? you have stated computer-assisted techniques allow engaging and fun activities (lines 99-104). Can this issue be generalized?

Again, this comment connects with a similar comment of reviewer one.

First rehabilitative approaches may be different depending of health professional. So, we changed a little bit the sentence line 99. For line 103-104, we agree that the first part of the sentence suggest a generalization that may not be true in a real-world clinical setting and that the second part may be a shortcut to suggest potential indirect reduced cost related to rehabilitation care by heath professional. Accordingly, we have largely modified this paragraph.

I would link the paragraph starting in line 105 to the previous paragraph.

The two paragraphs are now linked.

I would link the paragraph starting in line 129 to the previous paragraph.

The two paragraphs are now linked.
In the abstract, you detailed one week after the end of the intervention. However, in the design section, you state "...two weeks after the end... Please, revise this part of the text.

This is a mistake. Short-term assessment take place within the week following the end of intervention. This has been corrected

I would delete the next sentence included in line 145: "...for assessments (screening, baseline, short and long-term retest)." This sound reiterative.

This part of the sentence has been deleted.

Please, include a "limitation section" at the end of the discussion section, detailing the possible limitations of your study.

As recommended by the reviewer a limitation section has been included at the end of the discussion.