Author’s response to reviews

Title: The effectiveness of ICT-based neurocognitive and psychosocial rehabilitation programmes in people with mild dementia and mild cognitive impairment using GRADIOR and ehcoBUTLER: study protocol for a randomized controlled trial.

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Author’s response to reviews:

1. Please, change the sentence in the Introduction “Similarly, a review by Clare and Woods reported no significant effects of cognitive trainings, although the cognitive rehabilitation approach in people with Alzheimer’s disease and vascular dementia is promising and more RCTs are needed [11].” To “Similarly, a systematic review by Clare and Woods reported no significant effects of cognitive trainings interventions; while the only study on cognitive rehabilitation included in the review found preliminary but promising results of this approach when applied in people with Alzheimer’s disease and vascular dementia [11].”

We thank the editor. This was changed in the manuscript.

2. The inclusion criteria based on MMSE is still confusing, with inconsistency between text and table 1. The reviewer’s understanding is that the MCI and mild dementia diagnoses are based on CDR scores. MMSE is meant to refine the severity of the patients who will be eligible to the study. The reviewer’s previous suggestion was to set an inferior threshold, i.e. to include MCI patients with a MMSE of at least 27. Please definitely clarify how the MMSE will be used to define the study participants, also considering that recruitment should have been also started (according to the timeline provided by the authors at submission) – so, what MMSE criteria were used?
Participants will be selected based on the Petersen criteria and MMSE, which in this case is a support scale for including people with MCI. People with MCI must have cognitive problems without functional changes. MMSE is a screening instrument for detecting cognitive problems and we will be using the threshold of 27 points as suggested. Therefore, participants with an MMSE over 27 cannot be included. However, the MMSE cannot be used as the main or only diagnostic tool. Moreover, the CDR scores are a confirmatory scale of the previous criteria. Therefore, the use of CDR is for confirming the main inclusion criteria diagnosis-related and the MMSE is an additional tool for applying the diagnosis criteria.

We apologise for the confusion in the arithmetic signs “≤” which was inconsistent between the table and the main text.

3. Why was “Current antipsychotic medication and/or cognition affecting medication” now included among the exclusion criteria? Cholinesterase inhibitors are “cognition affecting medications”. Does it mean that patients receiving them will be now excluded? If, as they said, the authors meant to assess the effect of the study interventions on the top of the usual therapy received by these patients, the editor does not see any issue with including these patients, since the randomization will distribute them evenly across groups.

In the main text paragraph, it is stated that cholinesterase inhibitors and memantine are permitted if they have reached stabilized doses. The antipsychotic medication is in the exclusion criteria because these can influence the results of the assessment tests and can be a confounding factor for the diagnosis. The aim is to avoid the use of medications influencing cognitive or functional skills, not drugs regularly used in these disorders.

4. The sample size calculation is still cryptic. How was the number 400 obtained? Is this simply a convenient sampling? If so, it might be stated as it is. Otherwise, what does it mean a “maximum” sample size? Is it “maximum” based on capacity, i.e. the maximum number of patients that can be enrolled based on study resources, funding, etc.? Then, the equation and its explanation are unclear; what was the equation used for?

We calculated the sample size in a mathematically correct way. We set up an upper threshold of 400 participants recruited due to the logistic and management reasons. However, we consider the calculation of the effect size justifiable as it is in concordance with other studies of cognitive interventions.

5. Usability study. Please, explain in the manuscript what the experimental phase of the usability study consists in, and who and how many are going to participate.

We expanded this part of the manuscript. Experimental phase refers to the collection of all incidents during the RCT connected with the use of both programmes (GRADIOR and ehcoBUTLER).
6. We thank the authors for the specification of the primary outcome and of the statistical method they are using to analyze it. However:

   a. In the “Primary outcome measures” section, the authors should modify the following sentence accordingly: “The change in cognitive performance after a period of 4 months and 12 months in comparison with baseline results will be measured in all study groups using the Spanish version of the Mini-Mental State Examination (MMSE). This consists of 35 questions [37] and an ADASCog Cognitive Subscale [36] which evaluates cognitive performance in memory, praxis, orientation and language.” If the ADASCog Cognitive Subscale is the primary outcome, its change over time should be the primary focus.

   We want to thank the reviewer for pointing out this contradiction in the text. We have now rephrased the sentence to be consistent. The MMSE will be used as an additional measure for cognition as this scale is commonly used in cognitive intervention studies. We consider ADASCog a better instrument but we wanted to use the MMSE for comparing our results with other clinical trials in this population.

   b. In the statistical analysis section, the following sentence does not make a clear sense “For normally distributed data the Repeated Measures ANOVA will be used to examine the hypotheses in intersubject and intra-subject analysis as well as in their interaction.” “Interaction” between what?

   This interaction refers to the analysis of the different responses or evolutions of the 2 groups of subjects (PwD and MCI) or 4 treatments over time (throughout all the measures collected from the dependent variable). Therefore we will conduct a comparison within and between the treatment groups in the collected measures as well as the comparison between the condition and interaction between treatment and each condition in all collected measures.

Reviewer reports:

Reviewer #3:

Dear Editor, The authors have made many corrections to their original manuscript. The current version of the article has surely ameliorated. I have not further relevant remarks. See only some minor corrections listed below. I believe that the manuscript is now acceptable for publication in TRIALS.

Page 7, lines 48-49: in MCI participants should have CDR = 0.5 (NOT < 0.5; see the same error with CDR in the table 1, below).

We thank the reviewer. This was changed in the manuscript.
Page 8, lines 20-21: MMSE score, defined by a cut-off point of $\geq 26$ points for MCI (NOT $\leq 26$) and $20 < x < 25$ points for people with mild dementia (NOT $\geq 25$). See the same error in table 1 at page 9.

MMSE Cut-off points for MCI: score has to be less or equal to 27, therefore $\leq 27$.

Page 9, lines 51-52: the parenthesis (what questionnaires?) should be deleted.

We thank the reviewer. This was changed in the manuscript.