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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The effectiveness of ICT-based neurocognitive and psychosocial rehabilitation programmes in people with mild dementia and mild cognitive impairment. A randomised controlled trial using GRADIOR and ehcoBUTLER.

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Editor’s comments

1. what is the primary study hypothesis and objective?

Currently, this is defined very vaguely. To say that “the intervention(s) will be considered successful as long as it (they) will affect one cognitive domain” does not sound a scientific question/hypothesis, not sustained by a specific rationale, and, above all, of arguable clinical relevance. This point is of paramount importance also considering that some of the authors declared to have conflicts of interest.
This is then strictly related to the choice of the outcomes and to the sample size calculation. It is currently unclear what the primary outcome is. What the sample size calculation was based on is also unclear, as unclear is the statistical approach used for the calculation. Please, clarify.

The primary outcomes measure session was reformulated. ADASCog will be the primary outcome measure for our primary aim which is changes in cognitive performance. The sample size calculation cannot be based on any previous results with GRADIOR which was considered in the section. The calculation was explained and expanded upon in the manuscript.

2. Some concerns have been raised by one of the reviewers with regards to the definition of participants and settings. The main editor’s concern is not related to risk of confounders (e.g. the effect of anti-dementia drugs that patients are allowed to take, or the effect of the natural history of the disease), because randomization should protect against it or at least minimise. Conversely, the choice of multiple different settings (i.e., “community centers, Memory clinics, Public hospitals, day-care centres and residential centers”) makes the implementation of the study difficult to imagine, and the results difficult to interpret. Please, clarify the following points:

- how many patients from each setting will be included? Will the randomization be centralised? Will the randomisation be stratified by-centre?

We will use simple randomisation which will be centralised. In each of the collaborating sites, potential participants will be identified and subsequently randomised to each intervention group. At this moment it is difficult to estimate the proportion of participants who will be recruited from each site or centre. However, we assume that the numbers will be similar across sites.

- how will the intervention(s) be effectively implemented? Will each patient provided with a tablet? Will the software be installed in the local computers?

This will depend on which treatment group a participant is allocated to. Participants in the GRADIOR group will be assigned to the nearest treatment site (e.g. memory clinic, primary care centre etc.) with access to the touchscreen device with GRADIOR installed. If a participant has a touchscreen computer the software will be installed on their device. For the ehcoBUTLER group, participants will be given access either to the platform from their own computer, or a computer at the closest treatment site, or they can be given a tablet with the access to ehcoBUTLER.

- in which way the intervention(s) will be implemented in “public hospitals”? will it be offered to outpatients or inpatients?

The Provincial Hospital in Zamora has a specialised ward with access to computers with GRADIOR software and ehcoBUTLER. The interventions will be offered to the hospital outpatients.
Then, please, clarify the use of the MMSE among the eligibility criteria. The way it is described now (i.e. only among the exclusion and not among the inclusion criteria, and mentioned only in the table and not in the text) has generated some misunderstanding among the reviewers.

There was a mistake in including the MMSE score as an exclusion criteria. This will actually be one of the inclusion criteria.

3. Usability study. Please clarify what the usability study will be used for, how it will affect the design of the RCT.

The usability study consists of three phases: pre-experimental (focus group, user testing and usability questionnaire), experimental phase (collection of incidents – problems with the programme) and post-experimental (user experience questionnaire). During all the phases we will identify possible problems related to the characteristics of the programs GRADIOR and EhcoButler and propose changes to them, both before the experimental phase begins and also after this phase.

4. Outcome assessment at 4 months. Please clarify the reasons for it. Will this be formally an interim analysis? The authors mention its importance in case of “lack of efficacy”. What does this mean? Did the authors pre-specify rules to stop the trial early?

The outcome measures collected at 4 months will serve as an interim analysis and at this point of the treatment the GRADIOR sessions will be adjusted in difficulty according to participants’ performance. Regardless of the results, the trial with all the participants will continue. Based on previous results, clinical trials with cognitive interventions are usually short-term (maximal duration around 6-7 weeks) (Hill et al., 2016). We would like to be able to compare the results from our long-term and short-term treatment and their different impact on the outcome measures.


5. Statistical analysis. This section does not describe clearly the method that will be used for analysing the primary outcome.

This part was corrected. We will use Repeated Measures ANOVA.
6. “Choice of comparators” section. The section defines interventions and comparators ambiguously, compared with the rest of the protocol. The section can be removed, as long as the study arms are clearly defined in the rest of the text (see also reviewers' comment).

This section was removed.

7. In the “Exit strategy” section, the authors start defining the study as a pilot. Please clarify.

This was an error. We apologise. Pilot referred to the study (the RCT).

Reviewer reports:

Reviewer #1:

This overall a well written paper and addresses a important and clinically relevant topic.

Here are some specific comments that I think would improve the paper.

1. The background section makes a point of emphasizing cognitive rehabilitation p 1 line 38 as a more effective than cognitive training, but the paper does not continue to explore this framework. I think this distinction may be the most innovative part of the paper and it would allow the technology advocated in the paper to be practically translated in a variety of clinical conditions not just MCI and age related cognitive decline. The word "effective" should be carefully defined, especially since the background section mentions the potential benefits of the GRADIOR to both PwD and also their caregivers (formal? Informal, paid?) etc.

The section mentioning the difference between cognitive training and rehabilitation has been expanded although the evidence is limited and more research in this area is necessary. We expect most of the caregivers in this RCT to be informal, although formal carergivers will also be included.

2. Intervention related issues:

The exclusion /inclusion criteria are well defined, however, I am wondering whether the possibility of recent hospitalizations (past 6 months) for other comorbidities (e.g., MI or stroke) should also be included as exclusion criteria, for a variety of reasons. The sample size calculations assume a 15% drop out, but it is likely to be 20% for the targeted age group. The outcome measurements are well defined except for the most important one: MOOD which appears to be left to the tester, without defining the time of day the testing will be performed! Finally, ethically it is perhaps important to consider the option of "participatory research" model since since I doubt that full PwD consent can be given.
Recent hospitalisation for stroke was included in the exclusion criteria. The previous studies with this population were conducted considering 15% drop-out rate (Orrell et al., 2014). The symptoms of depression will be measured using the Geriatric depression scale at the same time of the day as all the other outcome measures. Testing will usually take place in the morning or in the afternoon, depending on participants’ availability. People with mild dementia are most likely to be fully aware of their participation and are able to give informed consent. Every procedure as well as the purpose of the study will be clearly explained to all the participants.


Reviewer #2:

This article is very interesting for the potential readers in such field. But some information of the article is a little confusing. Such as the followings, page 2 line 37"the trial will compare the cognitive rehabilitation treatment using the GRADIOR programme with a psychosocial stimulation intervention (PSS) using ehcoBUTLER platform, with a combined treatment consisting of GRADIOR and ehcoBULTER, and with a group receiving treatment as usual during a period of 1 year" might be revised as "Difference of the cognitive rehabilitation treatment strategies will be explored among 1) only GRADIOR programme; 2) only psychosocial stimulation intervention (PSS) using ehcoBUTLER platform; 3) combination of GRADIOR and ehcoBULTER; 4) and common treatment as usual for one year."

The trial concerns differences of effectiveness of cognitive rehabilitation AND psychosocial stimulation AND combined treatment not only cognitive rehabilitation strategies what was suggested. We maintained the original formulation.

The same page line 50 "one year of follow-up is planned to investigate the lasting effects of the conducted treatments" might be changed to "And then all the participants will be followed up for one another year to explore the potential long-term effects of these treatments". Some places should be corrected in order to increase the readability of the manuscript. And since this article focused an interesting topic about the cognitive rehabilitation, the abbreviation should be given with the full-term as they appeared at first in the article, which will help the readers to understand the topic easily.
The trial will compare the effectiveness of the cognitive rehabilitation treatment with GRADIOR programme with other types of treatment. The formulation of the follow up study was changed and full abbreviation description was added.

Reviewer #3:

I believe that the article by dr. Martina Vanova and co-authors needs a thorough revision before it would be acceptable for publication in TRIALS. I suggest a re-submission after a comprehensive review. For clarity, I listed my main remarks by following the order of the manuscript sections.

Introduction/Background

-The authors didn't explain the difference between cognitive rehabilitation and cognitive training. Definition and reference added to the introduction.

-A comprehensive review of positive data about computerized cognitive training in MCI has been showed, but no previous studies about computerized cognitive training in mild dementia are reported. The recent revision and meta-analysis about computerized cognitive training in MCI and dementia by Nicole et al. (American J Psychiatry, 2017; 174, 4, April) could be included.

We have added the reference considering the suggested results. More results of computer-based cognitive interventions in PwD were already mentioned in the introduction.

-The presentation of GRADIOR and especially of echoBUTLER in the Background section is quite scant. I believe that some general information could be anticipated from Procedure and intervention part.

More information was added to the ehcoBUTLER description.

-Some sentences sounding as commercial rather than scientific should be avoided (e.g., "The GRADIOR programme has been successfully used in Spain and also in English speaking countries in over 450 centers in the social and health sector"). This is a critical remark considering that first, second as well as the last author of the manuscript have declared competing interests in this work.

This part was omitted and reformulated.

-The term subdomain is incorrect (memory, attention, etc. are cognitive domains).

Corrected
Methods

-(Design) The full study timeline is described in table 2, not in table 1.

-(Participants) Suitable MCI and mild dementia participants will be identified at various sites, i.e., Community centers, Memory clinics, Public hospitals, day-care centers and residential centers. In this case, I wait for clinical diagnoses to be very heterogeneous between different recruitment sites. In particular, clinical diagnoses are usually supported by advanced examinations in memory clinics (e.g., neuroimaging, biomarkers analysis, genetic data, etc.), but less frequently in other sites. So, I believe that the study should include a phase in which some expert clinicians accurately revise the medical charts to document the diagnostic workup performed. Moreover, some criteria should be adopted to make the diagnostic accuracy more homogeneous among different recruitment sites (e.g., by considering a minimum data set that includes detailed history taken from relatives, at least an MRI examination, extended neuropsychological assessment, etc.).

The DSM V diagnostic criteria for dementia and Petersen criteria for MCI will be adopted at each diagnostic identification of suitable participants. We believe that these criteria are homogeneous enough to identify participants with the required diagnosis. Although recruitment sites can have an influence on different aspects of participants’ lives, the final diagnosis (MCI or dementia) should not be affected.

-MCI is equivalent to a CDR score of 0.5 (=0.5). CDR scores < 0.5 correspond to people with unimpaired cognitive status (i.e., normal or healthy). Moreover, mild dementia participants have CDR score >=1 and <2. CDR score of 2 (=2) corresponds to moderate dementia.

-Current significant neurological disease in exclusion criteria has to be defined more precisely. Also, mild dementia and MCI could be defined as neurological diseases. I suggest reporting a more accurate and definite list of the neurological diseases excluded in this study (e.g., history of epilepsy, traumatic brain injury, multiple sclerosis, Parkinson's disease, Huntington's disease, etc.). Moreover, I don't understand why Lewy Body dementia has been excluded. The extrapyramidal syndrome in DLB is often very mild and could be absent at presentation or in early stage of dementia. Furthermore, I believe that it is challenging to have a valid diagnosis of DLB when patients are in an MCI stage. So, it is complicated to exclude MCI-DLB patients in a sample of MCI patients.

The list of significant neurological diseases was expanded upon to include mentioned examples. However, it would be difficult to mention all conditions. We consider a significant neurological disease as any condition which could significantly influence or alter participants’ cognition. Regarding the DLB, the specific features often present in the diagnosis e.g. visual hallucinations, fluctuations, Parkinsonism etc. might require a different approach. Furthermore, the prevalence of this type of dementia is usually very small (4%) (Clare et al., 2013).

-Why have only antipsychotic medications been excluded? What about the multitude of other drugs with possible effects on cognitive status? (e.g., benzodiazepines, antiepileptic drugs, anticholinergic drugs, opioid analgesics, chemotherapy drugs, etc.).

Because despite being forbidden or often considered inappropriate for most people with dementia, there is still a high usage of antipsychotic medications. The aim of the study is to use non-pharmacological interventions as a complement to the regular intervention, but we cannot allow the use of a broadly used medication which is not properly recommended. Although other types of medication mentioned above can influence cognitive status, the randomisation should make the distribution of these people equal between the treatment groups.

-Voluntary participation is probably a limit of the study because some recruitment biases are added (e.g., overall patients with high motivation, or who have already had participation on a trial, etc.). This fact should be discussed in the Discussion section.

Any participation in the study is voluntary regardless of the group each participant is assigned to.

-The concurrent use of cholinesterase inhibitors and memantine in the experimental groups is a severe problem. How can we be sure of an ultimately positive effect of cognitive training on MCI or early dementia, if patients concurrently take medications which could enhance cognitive functions by themselves? And what about the interaction and the combined effect of cognitive training with cholinesterase inhibitors and memantine on cognition? The fact that participants must have been stabilized on their current dose for a minimum of one month before the baseline assessment seems not to be a sufficient condition to ensure that any changes will not be confounded by medication effects. At least, a strict control on assumption of these medications should be assured in the study (e.g., accurate report of time and doses of assumption, etc.). Moreover, a sub-analysis of the cognitive training effectiveness should be planned, which compares the results by patients without cholinesterase inhibitors and memantine with those who assume these medications.

We will use a control group so we will compare: patients taking drugs for dementia versus patients taking these drugs plus receiving the psychostimulation/ cognitive rehabilitation technological-based intervention. We want to know the usefulness of this technological approach when added to the usual care (including pharmacological treatment if necessary), but not versus pharmacological treatment. Of course, we will have a strict control and report the usage of these medications (many items are included in the InterRAI HC tool, e.g. starting date, time taking, doses, side effects, adherence, etc.) and at every appointment, the side effects, adherence and doses or any changes will be reported.

-The additional criteria for MCI based on MMSE score are disputable. MMSE, in fact, is not a proper test for MCI (see for example Alex J. Mitchell (2013). The Mini-Mental State Examination (MMSE): An Update on Its Diagnostic Validity for Cognitive Disorders, in A.J.
Larner (ed.), Cognitive Screening Instruments, 15 (Chapter 2: pp 14-46) DOI 10.1007/978-1-4471-2452-8_2. Springer-Verlag London 2013). Other different tests, e.g., MOCA test, are considered more appropriate. Moreover, in my clinical experience, I met many MCI patients who had a MMSE score between 26 and 30. So, a cut-off point of <=27 for MCI maybe not a good criterion. For MCI I suggest inserting only the inferior cut off (MCI should have MMSE score>26). MMSE score <25 for mild dementia participants is correct. Nonetheless, it should also be >20, because MMSE score <20 correspond to moderate dementia.

Cut-off scores for both groups were adjusted.

-Table 1: CDR score for MCI should be only =0.5. For mild dementia patients >= 1 and <2. See the previous point.

Error corrected.

Procedure and Intervention

-(Preliminary usability study) I believe that authors may describe the usability study more in detail. Moreover, I don’t understand if participants will be selected from the same sample of the effectiveness study or a different sample. Furthermore, I have some doubts on validity of results from a Focus group with mild dementia people.

A more detailed description of the usability study was added to the protocol. Participants will be selected from a different sample (although any of them may participate later in the experimental phase, if they meet the inclusion criteria).

It is necessary that people with dementia can articulate their experiences of using a software program. In the mild dementia phase, memory problems are evident but they do not significantly impact functional capacity. Communication and cognitive skills are more preserved. The literature reveals that the focus group method has been successfully used by researchers to interview people with mild dementia mainly [1, 2, 3].


-(Intervention, GRADIOR) Memory, attention, orientation, perception, etc. are not cognitive subdomains but cognitive domains. Moreover, reasoning and executive functioning are not different domains, but two distinct prefrontal functions.
This is how the exercises in GRADIOR are grouped and described in the programme. Memory, attention, orientation, perception, calculus, executive functioning and reasoning are the main groups of exercises which are later subdivided into subdomains e.g. visual iconic memory, sustained iconic attention etc. Please see a full list of different subdomains which was added into the Annex.

- It's important to report more details about cognitive functions stimulated by GRADIOR. To state only the name of a cognitive domain, e.g., memory, is insufficient. What memory type (episodic v/s semantic, anterograde v/s retrograde, etc.) and process (e.g., encoding, consolidation, retrieval) are especially trained by GRADIOR? What memory paradigm do GRADIOR use (e.g., delay recall, learning, recognition, etc.)? This fact may be particularly relevant when the authors interpret the results of the trial.

We included the list of all Types of exercises (called subdomains).

-(ehcoBUTLER) I believe that ehcoBUTLER can be showed a little more in detail.

More detailed description of the ehcoBUTLER platform was added to the introduction. ehcoBUTLER is a platform under development and despite being an European project, its description and functional details remain not fully specified.

-(Doses) I found a bit of confusion in doses reported for ehcoBUTLER (5 hours per week or more, or 2 hours per day?). Moreover, I don't understand why doses of GRADIOR as well as ehcoBUTLER in the combined treatment group (respectively 60 minutes/week and at least 180 minutes/week) are so different from those in both the group with single treatment (GRADIOR group: 90-120 minutes/week; ehcoBUTLER: 300 minutes/week). Also, the total time participants are involved in some activities is much different among the three treatment groups.

In this case we had to consider the practical aspects of each type of treatment and its possible impact on participants’ motivation, performance etc. The GRADIOR session is an intensive cognitive rehabilitation during which participants attention would be prone to decline if the sessions were longer or might be simply too tiring if these were more frequent. Regarding ehcoBUTLER, as it is more of a social engagement and stimulation tool, the approximate amount of time is difficult to estimate as it is not as structured as the GRADIOR treatment. Regarding the combined group, we were trying to find the most realistic balance for participants being included enough in both activities.

-There is poor control on the use of ehcoBUTLER. May it be improved in some way?

We described the control procedure for the use of ehcoBUTLER platform in more detail and have changed this in the protocol. We changed the control procedure from “writing to the Book of life” into completing certain tasks in “Task list”. Also, ehcoBUTLER does record certain data when being used. As ehcoBUTLER is still in development, certain characteristics and functionalities are not yet specified in detail.
- As the authors report in the last sentence of Method section, none can control or influence the interventions of participants in the control group (i.e., TAU, treatment as usual). Therefore, participants with TAU can participate in other cognitive rehabilitation or stimulation programmes.

I understand that it's not ethical to forbid any treatment for participants in a trial. But, I believe that authors should accurately take note of each additional treatment received by participants during the trial.

During assessments participants will be asked about any changes in their treatment and activities. There will be additional notes on their treatment considering any activities similar to any of the other treatment groups which could be a potential confounders. This was added into the protocol.

Treatment adherence

- It's customary to have trained clinicians (e.g., neuropsychologists, behavioral neurologists, trained nurses or therapists, etc.) for an accurate administering, scoring, and interpretation of neuropsychological tests. This remark is even more important considering that participants will be not healthy people, but MCI as well as mild dementia patients. Moreover, the idea that unidentified interviewers can fruitfully manage a cognitive assessment for MCI and mild dementia participants after having access to some video guidelines is unacceptable.

The interviewers will be trained clinical psychologists or neuropsychologists. This was changed in the protocol.

Outcome measures and hypotheses (+ analysis)

- I think that the cognitive domains evaluated in the study and the list of tests selected for each domain may be shown more clearly. Moreover, what and how many tests have been selected for each cognitive domain? What criterion has been adopted to establish when a cognitive domain has improved or worsened, e.g., improved score at a single test? Two tests of three improved? All tests of a specific cognitive domain improved? And what conclusions can be drawn when a single test score has improved, and concurrently other tests of the same cognitive domain have worsened?

To assure possible generalisation of GRADIOR’s impact on cognitive abilities, we have selected a variety of tests (for partial cognitive functions as well as for general cognition – ADASCog) which might not be linked directly to GRADIOR’s functions or domains to ensure that GRADIOR (or ehcoBUTLER) treatment’s effect is transferable and generalizable. GRADIOR provides options to assess the scores in each task for each participant but we want to see its impact on cognition, and not solely whether the participants improved in the tasks. The cognitive assessment tests selected cover a variety of tools mostly used in clinical practice. Participants’ scores will be evaluated separately for each test.
-When cognitive functions not directly stimulated by a cognitive training have improved, this fact is regarded as a relevant outcome of a cognitive training. Why did the authors not consider this option among the outcomes?

GRADIOR trains all sort of cognitive abilities. I do not understand which cognitive functions reviewer meant. We will evaluate the impact of all treatments on overall cognition as well as on partial functions.

-A post-training improvement in a test score is not enough to demonstrate that cognitive status has improved. Some other variables that could cause a score change when tests are repeated (many neuropsychological assessments have been planned in the timeline of this study, i.e., preliminary, at 4 months or midterm, at 12, 16 as well as 24 months) should be considered in interpreting cognitive status changes. More relevant factors are practice effects, psychometric errors due to low test-retest reliability, regression to the mean, effects of various demographic variables (I judge as seminal the work by TN Tombaugh on this topic; see, for example, taking into account the MMSE, Tombaugh TN, Archives of Clinical Neuropsychology, 2005; 20:485-503). In this context, in prof. Tombaugh words, "....analyses showing the average amount a group changes are not particularly helpful in determining how much an individual's score must change for it to represent a significant change".

Instead, analysis based on individual performance should be considered (e.g., a Reliable Change Index, see Tombaugh).

All tests used in the evaluation are officially validated on the Spanish population. We assume that conducting the assessments in 4 months’ time is enough to avoid learning by repetition. During the analysis we will consider score improvements (changes) per individual rather than changes in average score per group. We are using the same outcome measures during the whole study to be able to generalise the overall effect of every treatment throughout the study. As mentioned before, we are using different outcome measures in addition to GRADIOR’s tasks to be able to generalise its effect on cognition.

-It is well known that some MCI patients have a reversible course. Their cognitive performance improves at follow-up, and they don't show cognitive impairment anymore. Coming to the study by dr. M.Vanova et al., there is the relevant problem to distinguish the possible positive effect of the cognitive training from the "natural" cognitive improvement of some reversible MCI participants. To plan outcome based on single patient measures (e.g., the percentage of patients improved or responders) could be an option to control this bias (e.g., responders should be more numerous than reversible MCI participants).

-Rate and time of conversion from MCI to dementia could be other relevant outcome measures in this study. In fact, even if no positive changes in specific cognitive domains would emerge at the end of the trial, GRADIOR could be regarded as effective if lowered the number of MCI participants who convert in dementia or delayed their conversion moment.

In a more detailed analysis, we will compare the results of each of the 3 intervention groups with the TAU which will be a relevant comparator of the effect of each treatment. We will analyse the
number of cognitively improving people with MCI in cognitive rehabilitation groups in comparison with TAU. If this number will be significantly higher for the intervention groups than in TAU then we will consider the positive effect of the treatment of people with MCI. Regarding participant progression from MCI to dementia, this will also be analysed in more detail during the follow-up.

Secondary outcome measures

-I have many doubts on validity of questionnaires administered to mild dementia patients.

-"As GRADIOR focuses solely on cognitive rehabilitation, we assume that those participants with dementia receiving only the GRADIOR treatment will not see improvements in their quality of life, depressive symptoms, the quality of their relationships with a carer and/or activities of daily living after 4 or 12 months". Why the authors make such a pessimistic prediction? Spreading of benefits from cognitive training to other aspects of patient life, e.g., quality of lives, depression, etc., should be an hoped for result of this study.

Based on results from previous studies cited in the introduction that cognitive rehabilitation’s effect on quality of life or mood are inconclusive, we decided to apply this rather neutral hypothesis. GRADIOR focuses on cognition therefore we do not predict any effect on other aspects.