Reviewer’s report

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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Reviewer: Carlo Abbate

Reviewer’s report:

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.

-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.

-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.

-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.

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

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.).

-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.

-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.).

-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.

-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.
-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.

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

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.

-(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.

-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.

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

-(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 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.

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

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.

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?

-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?

-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).
-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.

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.

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