Author's response to reviews

Title: Evolutionary cognitive therapy versus standard cognitive therapy for depression: a protocol for a blind randomized, superiority clinical trial

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Author's response to reviews: see over
Response to review

“As suggested by the reviewer, the authors have NOT modified the manuscript title. It would be better to try something like: Is an evolutionary-driven psychological intervention better than cognitive behavioral therapy for patients with depression: protocol for a randomized clinical trial. Also Page 4, line 1.”

Author’s response: Following the reviewer suggestion and your recommendation, we have now changed the title from “A randomized trial for an evolutionary-driven psychological intervention for depression” to “Evolutionary cognitive therapy versus standard cognitive therapy for depression: a protocol for a blind randomized, superiority clinical trial”. In choosing the title, we took into consideration the SPIRIT guidelines for reporting clinical protocols (see also the next comment).

“Here is a list of other issues for the authors to consider.

1. It would be useful to have the authors follow the new SPIRIT guidelines for writing protocols.”

Author’s response: We have reorganized the entire manuscript to fit the SPIRIT guidelines for writing protocols. For that purpose we operated the following modifications within the manuscript.

a) We have changed the title from “A randomized trial for an evolutionary-driven psychological intervention for depression” to “Evolutionary cognitive therapy versus standard cognitive therapy for depression: a protocol for a blind, randomized, superiority clinical trial”. See also Page 4, lines 1-2.

b) Page 4, line 3: we changed the subsection title from “Background” to “Background and rationale”.

c) Page 6, line 20: In order to emphasize the study’s objectives, we introduced the following subtitle – “Objectives”.

d) Page 7, Line 5: We introduced the following subtitle – “Trial design”

e) Page 7, lines 6-8: We introduced the following phrase – “This study is designed to be a blind, randomized, superiority clinical trial. The experimental group receives an
Evolutionary-Driven Cognitive Therapy for Depression (ED-CT). The control group receives Cognitive Therapy for Depression (CT).

f) Page 7, line 12: We changed the section subtitle from “Methods/Design” to “Methods”
g) Page 7, line 13: We changed “Study Population and Recruitment” to “Study Setting”.
h) Page 7, line 14: We introduced the word “Romanian” to indicate that participants will be Romanian patients.
i) Page 7, lines 16-17: To clarify the location/site where the study will be implemented, we introduced the following statement – “The study is implemented in Cluj-Napoca, Romania, through the Babeș-Bolyai University Psychological Clinic.”
j) We reorganized the text in Methods section to better reflect the SPIRIT guidelines. In consequence, the order of paragraphs in this section is now as follows: Study Setting; (including Eligibility criteria); Interventions (including The CT group; The ED-CT group); Outcomes and measures (including Primary Outcomes; Secondary Outcomes; Other Outcomes; Measures of primary outcomes; Measures of secondary outcomes; Measures of other outcomes); Participants’ timeline; Sample size; Recruitment; Assignment to interventions; Data collection, management, and analysis; Monitoring study implementation.
k) We have reorganized the text and included a new section, namely “Ethics and dissemination” (P 24, p 3, line 12).

2. Page 1, item 1: There is a square box after [Babe] that is not clear. Is this a special symbol? Also list the location of the University as a city. Also P 7, p 2, l 8; Also P 8, p 4, l 2< Also P 9, p 1, l1. Also P 9, p 3, l5. Also P 18, p 6, l 1.

Author’s response: The square box appears because the word-processing software might not recognize a special character. The character is “□” (it reads Babeș-Bolyai University). We have corrected this throughout the text. If a square box continues to appear on your end, it can be safely replaced for „s” (a.k.a. „Babes-Bolyai University”).

The location of the university is now listed.

3. Page 1, l 2. Add [NY] at the end of the l. Also P 1, l 3. Also P3, l 4, l2 to replace [New York].
Author’s response: We have implemented the suggested replacements. (P 1, lines 23-26). However, “Upstate New York Health Care” is a part of the name of the institution, therefore we have not implemented the suggested change here.

4. P 2, p 1, l 2. Replace [significant] by [large] or a similar term. Save significant for a statistical context.

Author’s response: As suggested, the change has been made. (P 2, p 1, line 4)

5. P 2, p 1, l 6. Delete [in order] in front of [to] as the words are redundant in English. Also P 7, p 2, l 14. Also P 13, p 4, last l.

Author’s response: We operated the suggested modifications (Page 2, p 1, line 8, Page 12, p 2, line 12, Page 13, p 1, line 2).

6. P 2, p 2, l 2. Insert a space to read [> 13]. Also P 8, p 3, l 1.

Author’s response: We operated the suggested modifications (Page 2, p 2, line 13, Page 7, last p, line 21).


Author’s response: We reworded the sentences as follows: “This randomized trial compares a newly proposed Evolutionary-Driven Cognitive Therapy to a Classical Cognitive Therapy protocol for depression. To our knowledge, it is the first attempt to integrate insights from evolutionary theories of depression into the treatment of this condition in a controlled manner.” (see Page 2, p 3, lines 21-22; Page 3, lines 1-2).

8. P 3, p 2. Include the data of registration as well as the date the first patient was randomized. Was Nov 1, 2012 the date the first patient was randomized? See also P 20, p 5.

Author’s response: We added the following information:
“The trial was registered in June 2013. The first participant was enrolled on October 3, 2012.” (see Page 3, p 2, line 6).

“Participant recruitment began on November 1, 2012. Randomization of the participants was performed on September 27, 2012. The first participant was enrolled on October 3, 2012.” (see Page 26, lines 16-17).


Author’s response: As suggested, we operated the replacement (Page 5, p 2, line 8).

10. P 5, p 2, l 4. Since [or] logically includes [and], delete [and/]. Also P 9, p 3, l 5.

Author’s response: We operated the suggested modification (Page 5, p 3, line 12, P 20, p 1, line 5)


Author’s response: We operated the suggested modification (Page 6, p 2, line 7).

12. P 8, p 1, l 4. Delete [s] to read [drug].

Author’s response: We operated the suggested modification (Page 13, p 2, line 12).

13. P 8 ff. Have all the outcome measures being used in this study been validated for use in Romania? Cite the R(eference) for them. The scale for each outcome should be defined and how to interpret each end of the scale. The measurement properties needed for this trial should be specified numerically. This should be done for every outcome measure used.

Author’s response: Thank you for pointing this out. Most of the measures used in this study are validated on Romanian population - and which ones are those is now made clear in the current revision of this manuscript (see pages 13 – 14, Measures of primary outcomes, Measures of secondary outcomes, and Measures of other outcomes). We have now included complete descriptions of the scales, and, in the case of the scales that have not been used previously on the Romanian population, we now clearly explain how we come to the Romanian versions used in this study (see P 19, p 4, lines 11-15).
14. **P 9, p 3, l 1. Provide more detail of the randomization as per CL Meinert’s clinical trials book P 86.**

**Author’s response:** We have included more details about the randomization in the current version of this manuscript. The text now reads (see Page 21, p 3, lines 12-19) as follows:

“Assignment to interventions”

The participants are randomly assigned to one of the two conditions using a sequence generated by the software Randomizer.org. Randomization is performed by a research assistant using a simple (unrestricted) randomization sequence that assigns two unique numbers per participant; number assigned can range from 1 to 2, according to the number of experimental conditions. To conceal the allocation mechanism, the same research assistant puts the patient in touch with his therapist without revealing anything about the intervention protocol implemented by that therapist.”

15. **P 9, p 5, l 1. Provide a R.**

**Author’s response:** The paragraph in question has been reworded and now reads as follows (see P 14, p 3, lines 17 – 23, P 15, p 1, lines 1 – 2):

The Fitness Evaluation Scale (FES) is a scale adapted and expanded by the authors from the High-K Strategy Scale (HKSS) [49]. The HKSS has been shown to be negatively associated with depressive symptomatology [25] and psychopathology in general [23]. The FES consists of 45 items (58 if the patient has children) tapping into various dimensions theorized to make up the indicators of fitness. Participants rate every item on a five-point Likert scale. A total FES score is computed by adding up ratings for each item, with higher scores indicating greater fitness. The FES was preliminarily validated on a sample of 146 subjects and has shown good internal consistency (Cronbach’s alpha = 0.93). The FES is the therapist’s starting point in prescribing the evolutionary-driven interventions, as further detailed below.


**Author’s response:** We operated the suggested replacements (Page 14, p 2, line 11; Page 19, p 3, line 8).

*Author’s response:* We operated the suggested insertion (Page 16, p 2, line 13).

18. P 13, p 3. Is there going to be any blocking? Who will conduct the allocation set up?

*Author’s response:* We have now clarified these aspects in the “Assignment to interventions” subsection (P 21, p 3, lines 13 – 19). This paragraph reads now as follows:

   The participants are randomly assigned to one of the two conditions using a sequence generated by the software Randomizer.org. Randomization is performed by a research assistant using a simple (unrestricted) randomization sequence that assigns two unique numbers per participant; number assigned can range from 1 to 2, according to the number of experimental conditions. To conceal the allocation mechanism, the same research assistant puts the patient in touch with his therapist without revealing anything about the intervention protocol implemented by that therapist.

19. P 14, p 2, l2. Comment on whether this manual is going to be available from the authors and how.

*Author’s response:* To address this suggestion, we have inserted the following sentence – “Following the implementation of the study, the manual will be available upon request from the first author and will also be sent out for publication.” (see Page 8, last p, line 23 and Page 9, p 1, line 1).


*Author’s response:* We operated the suggested replacement (Page 11, p 3, line 15).

21. P 17, bottom. BMC Trials does not permit any footnotes. Make this in a R.

*Author’s response:* As suggested, we eliminated the footnote and transformed it in a reference (Page 23, p 1, line 4; Reference 94, Page 35).
22. P 18, p 2. This p does not contain alpha and there is no comment on how the multiplicity of outcomes is to be handled in the trial. Was any software used to compute the sample size? Cite it if Yes.

**Author’s response:** We now clarified these aspects in the “Sample size” subsection. The text now reads:

“Sample size”

An a priori power analysis based on a medium effect size estimation indicated we need a total of 100 participants (planned main statistical test: ANOVA – repeated measures, between factors; effect size: 0.247; statistical power: 0.80; a error probability: .05; 2 groups, 2 main measurements (pre- and post-intervention); correlation among repeated measures: 50). Power analysis was computed using G*Power 3.1.6 program [92]. Consequently, we randomized a total of 100 participants. Following the generation of the random numbers, we decided to use the first sequence of numbers for participants’ allocation in groups. This resulted in 43 participants randomized in the CT group, and 57 participants randomized in the ED-CT group.” (see Page 20, p 2, lines 7 – 14).

23. P 19, p 3. Cite the system you plan to use.

**Author’s response:** We have now clarified this aspect, as follows (see P 25, p 2, lines 5 – 8).

Finally, confidentiality and privacy are of paramount importance. The completed forms of the clinical instruments are kept in locked cabinets and the access to the electronic data is password-protected. The passwords are changed regularly and the clinical assessment reports contain no identifying information.

24. P 23 ff. Add date of last access (dola) to each R with a URL. R: 1, 12, 13, 36, 74.

**Author’s response:** As suggested, we operated the suggested modification (R 1, R 12, R 14, 45, 94, 95, and 97).


Author’s response: As suggested, we operated the suggested modification (Page 28, R 11, line 28).


Author’s response: As suggested, we operated the suggested modification (Page 30, R 20, line 15).

28. P 24, R 25, L 2. Insert volume and page numbers.

Author’s response: As suggested, we operated the suggested modification (Page 30, R 25, line 26).


Author’s response: As suggested, we operated the suggested modification (Page 30, R 28, line 33).

30. P 24, R 29. L 2. Rewrite as [DC]

Author’s response: As suggested, we operated the suggested modification (Page 31, R 36, line 15).


Author’s response: As suggested, we operated the suggested modification (Page 34, R 72, line 9; Page 34, R 75, line 16).

32. P 27, R 73. Insert location.

Author’s response: As suggested, we operated the suggested modification (Page 31, R 31, line 6).
33. P 28. Figure 1. Make the numbers here correspond to P 18 where 140 is used. Also cite the CONSORT R for the study flowcharts.

Author’s response: As suggested, we operated the suggested modifications (see Page 37). See also author’s response to reviewer’s comment 22.