Reviewer’s report

Title: Darwinian-driven cognitive therapy for depression: A therapy protocol

Version: 2 Date: 17 September 2013

Reviewer: Tara Donker

Reviewer’s report:

This papers describes the design of a RCT aimed to develop and examine an evolutionary-driven cognitive therapy protocol for depression. While evidence-based treatments for depression exist, a substantial amount of patients do not respond to this. Therefore, efforts to improve evidence-based treatments are important. The current clinical trial is designed to contribute to this desideratum. The manuscript is well-written, and is well-organized. The manuscript provides an account of the rationale and methodology of a study. However, a detailed account of the hypothesis has not been described and some methodological details are not provided.

1. Will the study design adequately test the hypothesis?

The trial aims to compare the effect of an evolutionary-driven Cognitive Therapy (ED-CT) to Cognitive Therapy (CT). The study has been set up as a randomized controlled trial. As mentioned previously, a detailed description of the hypothesis is lacking. Therefore, I cannot assess whether the study design will adequately test the hypothesis.

Because the two conditions are both active treatments, the design will be a (randomized) non-inferiority, equivalence or superiority trial (e.g. is one treatment non-inferior, equivalent or superior to the other treatment?). Since the authors state that the trial is designed to contribute to the efforts to improve evidence-based treatments, the appropriate design of the study would be a superiority trial, with the hypothesis that ED-CT will be superior to CT.

2. Are sufficient details provided to allow replication of the work or comparison with related analyses: if not, what is missing?

The method section contains detailed information and is well organized. However, a few details which are currently not described need to be added to allow replication of the work:

-Information on the background of the therapists giving CT and ED-CT and whether there will be different therapists for the two conditions? If not, there can be a contamination effect which will might bias the results.

-Training of assessors

-Plans to promote participant retention and complete follow-up is missing

3. Is the planned statistical analysis appropriate?

The power calculations seem to be appropriate for a RCT-design. However, the design of the study seems to be a superiority-trial. The power calculations and
needed sample size to reach sufficient power for a RCT, or a non-inferiority, equivalence, or superiority trial differ from each other.

Furthermore, the authors suggest using ANCOVA to analyze the data. However, given the different methods of data recruitment (several clinics, newspapers, etc.) which might attract different types of populations, and expected drop-out which could be analyzed with more sophisticated methods, I would recommend multilevel analyses (e.g. linear mixed models, mixed models repeated measures [MMRM]). The MMRM is able to account for correlations among repeated measurements for participants and can include participants with missing data. The MMRM use all available data and yield unbiased and efficient estimates of effectiveness under missing completely at random (MCAR) and missing at random (MAR) assumptions.

Besides a possible power problem, and the lack of a description how to analyze mediators, I do not believe the authors can conduct mediator analyses with this type of design, due to the lack of a control-group (CT is an active treatment).

4. Is the writing acceptable?
The manuscript is well-written and acceptable for publication.

Notes to the author

Major Essential Revisions

1. Please add a detailed account of the hypothesis to the manuscript.

The trial aims to compare the effect of an evolutionary-driven Cognitive Therapy (ED-CT) to Cognitive Therapy (CT). The study has been set up as a randomized controlled trial. Since the authors state that the trial is designed to contribute to the efforts to improve evidence-based treatments, should the appropriate design of the study not be a RCT, but a superiority trial, with the hypothesis that ED-CT will be superior to CT? When the two conditions are both active treatments, the design could be a (randomized) non-inferiority, equivalence or superiority trial (e.g. is one treatment non-inferior, equivalent or superior to the other treatment?). If so, this will have implications for the sample size needed to achieve sufficient power.

Minor Essential Revisions

Title:

2. Please add the design of the trial to the title (e.g. RCT, superiority trial?)

Abstract:

3. Methods/design: please include with which diagnostic instrument diagnoses are assessed

Methods:

4. CT and ED-CT: Please provide information on the background of the therapists giving CT and ED-CT (e.g. their educational background, specific training for the CT and ED-CT). Will there be different therapists for the two conditions? If not, there can be a contamination effect which might bias the
results.

5. Will the doctoral level clinical psychologist undergo SCID training? How will training take place of the diagnostic interview?

6. Please move CSQ and other information about instruments and assessment times from the ED-CT group description to the instrument/assessment section.

7. Please report on any plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols.

8. The power calculations seem to be appropriate for a RCT-design. However, the design of the study seems to be a superiority-trial. The power calculations and needed sample size to reach sufficient power for a RCT, or a non-inferiority, equivalence, or superiority trial differ from each other. Also, please justify the effect size $d=0.45$. For two active treatments, a between-group difference of $d=0.46$ at post-test is quite large. This trial might suffer from power problems.

9. The authors suggest using ANCOVA to analyze the data. However, given the expected drop-out and more robust assumptions to estimate models, I would recommend using more sophisticated methods, such as GEE or mixed models (linear mixed models, mixed models repeated measures [MRMM]. The MMRM is able to account for correlations among repeated measurements for participants and can include participants with missing data. The MMRM use all available data and yield unbiased and efficient estimates of effectiveness under missing completely at random (MCAR) and missing at random (MAR) assumptions.

10. The method to assess mediators is missing (e.g. what do the authors expect which variables are mediating? Which analyses will be used?). Also, I wonder whether there will be sufficient power to assess mediators. Did the authors perform a power calculation for this? Besides this, only mediator analyses can be performed when there is a significant difference between the two active treatments at post-test.

Minor issues not for publication

11. There are some typographical errors and grammatical throughout the manuscript.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.