Author's response to reviews

Title: Study on Psychoeducation Enhancing Results of Adherence in patients with Schizophrenia (SPERA-S): Study protocol for a randomized controlled trial

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Version: 8 Date: 17 August 2013

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Revision R2

 Replies to the reviewers

Thank you for forwarding the reviewers’ comments and for giving us the opportunity to further improve our submission. In the sections below we have addressed each of the comments made by the reviewers. Changes to the original submission are highlighted in the text using a red font.

Reviewer: Charlie Goldsmith

The following issues are raised in this version of the manuscript.

5. P(age) 1, listing of locations of authors. This is duplicated at the bottom of P 18 and the top of P 19. Once is enough!
   a. Listing of locations on page 1 was cut.

6. P 2 and 3 contains a new list of names with no comment as to why they are there. Without a justification, they should be deleted.
   a. The list of names refers to the investigators of the study. We removed this list and added it back in the acknowledgements section.

7. P 4, p(aragraph) 2, l(ine) 3. Add an [s] to [permutation] to read [permutations].
a. Edited as suggested.

8. P 4, p 4, l 4. A justification should be provided for measuring blinding given the Sackett R(eference) in the last review. Also P 10, p 2.

a. The main outcome of the study is adherence to the prescribed therapy, and one of the indicators is the measurement of blood levels of the primary prescribed drug, which is independent from the assessment carried out by the raters. It is unlikely that any personal opinion of the raters on the presumed superior effectiveness of one psychoeducational method over another will influence the measurement of blood levels of the primary prescribed drug. However, we are interested in knowing whether any bias had occurred in the blinding, whether by unintentional disclosure of the treatment condition or because the personal opinion of the raters led them to guess the patients’ allocation to the treatment modality.

b. The Cochrane collaborative group specifically stated “Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.”.

c. Contrary opinions to Sackett were also reported (see Shapiro S, Fergusson D, Glass KC. Substituting placebo for established, effective therapy: why not? CMAJ. 2010 Nov 9;182(16):1749-53. doi: 10.1503/cmaj.090548), strongly advising against the decision of the CONSORT statement (2010) to eliminate the item on how the success of blinding was assessed, although the empirical evidence cited for doing so is weak (reference to one study only: Schulz KF, Grimes DA. Blinding in randomised trials; hiding who got what. Lancet 2002;359:696–700).

9. P 5, p 3, l 2. Provide the date the first patient was randomized.

a. We added this information.

10. P 6, p 3, l 7. One would expect the relapse rate for controls to be higher than the intervention group. Is this the correct order?

a. The reviewer is right. We reported the percentage of relapse in an inverted order. This passage has been corrected.

11. P 7, p 2, l 8 to 10. No methods are provided to validate these instruments with the lab values. This should be part of the protocol for those self-report measures that are currently not well validated.

1. 12. Spearman’s rho will be used to compare blood levels of the main drug with the self-report or the interview; partial correlation will be used to ascertain the links between blood levels of the main drug with the self-report or the interview by taking into account the other measure (the interview or the self-report, respectively). This is now specifically stated in the data management and analysis section of the manuscript.
12. P 8, p 3, l 3. Rewrite as […, with a 1:1 allocation ratio.].
a. Edited as suggested.

13. P 8, p 4, l 3. Rewrite as [… months; admitting ages …].
a. Edited as suggested.

14. P 8, p 4, l 8. Rewrite as [be stratified by location, …]. Also P 9, p 5, l 4.
a. Edited as suggested.

15. P 10, p 4, l 6. Should another word besides [warm] be used here?
a. We substituted “warm” with “comfortable”

16. P 11, p 2, l 6. Is there a R for the 70%?
a. No, there is no reference for this criterion. This criterion was arbitrarily chosen after discussion within the study team.

17. P 11, p 5, l 1. Suggest rewriting as [- which could be the …].
a. Edited as suggested.

18. P 11, p 6. Beginning here there should a citation for each measurement instrument mentioned, a R for the Italian version if there is one and how they were validated in Italian. A table might be the best way to show this. Translation alone is not considered to be adequate. Interpretations for each instrument are also needed.
a. For each instrument, a reference for the validated Italian version was provided. All references relate to standard validation study, and all studies were carried out in clinical samples. The interpretation of the scores for each instrument was provided.

19. P 12, p 2, l 2. Replace [proportion] by [percentage].
a. Edited as suggested.

20. P 12, p 3, l 2. Is R 34 a good source for CGI or just DOTBS?
a. Reference 34 is considered the standard reference for both the CGI and the DOTES.

a. We were not able to understand to which instrument the reviewer was referring.

22. P 15, p 4 and 5. This is a different form for Cohen’s effect size, how is It different from the one used on P 6?
a. Since the power analysis was done by taking into account a difference by proportion, the Cohen’s h was used instead the Cohen’s d, which is based on a difference by a continuous variable. The Cohen’s h measures an effect size that
can be assimilated to the Cohen’s d.

23. P 16, p 3. Provide Rs for each test and specify the software you plan to use for each.
   a. All analyses will be done with Excel or SPSS version 17.

24. P 17, p 2. Provide Rs for these safety measures.
   a. We do not understand the reviewer’s comment. Suicide and suicidal attempt as a safety measure in a trial are standard.

25. P 17, p 2, last l. [CRF] is not defined on P 18.
   a. CRF refers to Case Report Form.

26. P 18, p 2, l 3. Rewrite as [20% for dropping out.].
   a. Edited as suggested.

27. P 18, p 2, l 4. Replace [multivariate] by [multivariable].
   a. Edited as suggested.

28. P 24, R 63, l 3. Rewrite as [(Italian)].
   a. Edited as suggested.

   a. We decided not to delete the section on blinding for the reasons already provided in the manuscript.

Reviewer: Sally Chan

The authors have revised the paper according to the majority of the reviewers' comments. I have the following comments:

1. I could not see a strong linkage between the psychoeducation programme and the primary outcome, i.e., medication adherence. Out of the 16 sessions, only one session discusses drugs. The rest is related to interpersonal and problem solving. If the authors would like to use medication adherence as an outcome, they need to strengthen the content of the psychoeducation on this component.
   a. Our hypothesis is that an improvement in the family climate and in family functioning and greater information on the drugs’ mechanisms of action and side effects might improve adherence to therapy as a result of better efforts of family relatives in supporting, guiding and supervising the patient.

2. The psychometric properties of the Italian version of the outcome measures should be reported.
   a. For each instrument, a reference for the validated Italian version was provided. All references relate to standard validation study, and all studies were carried out in clinical samples. The interpretation of the scores for each instrument was
provided.

2. Quality of written English: Needs some language corrections before being published
   a. We have had the manuscript revised by a professional mother-tongue English editor.