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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Author's response to reviews:

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

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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 now highlighted in the text using the red font.

Reviewer: Charlie Goldsmith

There are a series of issues that should be considered to improve this protocol.

1. P(age) 1, l(ine) 1. Suggest inserting [Patients with] after [in].
   a. Edited as suggested

2. P 4, p(aragraph) 2 does not mention the clustering or blocking suggested in the text.
   a. We added “by the method of blocks of randomized permutation”; clustering is implicit in the provenience of patients from 10 units.

3. P 4, p 3, l 4. It is not a good idea to measure blinding since it is usually not measuring blinding. See Sackett DL in Int J Epidemiol 2007;36(3):664-5. See also P 9, p 5.
a. We disagree with the reviewer. If assessors were more likely to correctly guess groups’ assignment, they could also have biased the evaluation towards the Falloon method, which is allegedly thought to be more effective than other psychoeducation methods. Conversely, if they cannot guess which group patients belonged to, they are unlikely to have biased the evaluation (positively or negatively) towards one method. We thought this is an helpful information.

4. P 4, last l. Include the date of registration and the date the first patient was randomized. If some recruiting has happened, state the current number recruited.
a. We added the date of registration of the trial; for organization problems, the date of recruitment was delayed to February 2013, and the randomization will start on June 2013.

a. Edited as suggested.

6. P 7, p 6. Did you consider stratifying by location? Clustering is not mentioned here.
a. Randomization will be based on stratification by location, due to the multisite nature of the study. Correctness of the randomization procedure will be monitored at regular intervals.

7. P 8, p 1, l 3. Suggest rewriting as [Admitting ages varying from 18 to 55 years.]. Also P 26, l 3.
a. Edited as suggested in both loci.

8. P 8, p 1. Consider adding the stratification and blocking to this p.
a. We added the information.

9. P 9, p 2, l 4. Cluster has not been defined and the randomization seems to be allocating individual patients, not clusters of patients. Provide R(eference)s to all methodology used.
a. All the patients will be randomized to the exposed (FPP) or the unexposed (GT) group with a 1:1 allocation ratio in each unit. Randomization will be based on stratification by location, due to the multisite nature of the study.
b. We did not understand what references the reviewer had in mind. These procedures are standard.

10. P 10, p 3, l 11. Delete [means of] since the words are redundant in English after [by].
a. Edited as suggested

11. P 11 and following. Many of the outcome measures are not cited with Rs and there are few with Italian versions with validation. These should be added if known. All measures should have the scoring summarized as well their interpretation. If there is a minimum clinically important difference (MCID) for
patients with schizophrenia then these also be added.
a. Measures with Italian validation were cited with specific references (e.g., ref. 34; ref. 38; ref. 40; ref. 44). We added some more references. Some of the scales were translated for this study. This is now explicitly stated. CGI and the DOTES are widely used tools, with standard translations available in many countries, Italy included, and local site studies are not usually cited.
b. Scoring methods were provided for all scales.
c. There is no agreed minimum clinically important difference in patients with schizophrenia for any of these tools. Findings from the CATIE study for the PANSS have been not replied in so far (Hermes ED, Sokoloff D, Stroup TS, Rosenheck RA. Minimum clinically important difference in the Positive and Negative Syndrome Scale with data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). J Clin Psychiatry. 2012 Apr;73(4):526-32).

   a. Edited as suggested

   a. Edited as suggested

   a. Edited as suggested

15. P 13, p 1, l 1. Replace [ranging] by [varying]. Also rewrite as [The scores in each domain vary from 4 to 20.].
   a. Edited as suggested

16. P 13, p 2, l 8 to 10. This does not appear to have been considered in the analysis section.
   a. Expressed emotion will be analyzed in both groups to evaluate whether one treatment or both will change it. In this case, data on expressed emotion will be entered in the analyses on the main outcome as a confounding factor.

17. P 14, p 1, l 4 and 5. Insert a space on either side the inequality signs.
   a. Edited as suggested

18. P 14, p 7. These analyses used here are not supported by Rs, and do not use cluster studies in their analysis.
   a. We were unable to locate the comment.

19. P 16, p 1 needs Rs for the methods.
   a. We were unable to understand the point of the reviewer. The section does not include any analysis.
20. P 17, p 1, l 5. Replace [parameters] by [variables]. A parameter is a characteristic for a distribution of a variable in a population, not another name for a variable in a sample.
   a. Edited as suggested

21. P 17, p 2, l 1. Since there is no literature search to support this phrase, suggest it be toned down to read as far the authors know.
   a. Edited as suggested

   a. Edited as suggested

   a. Edited as suggested

24. P 17, p 4, l 6 to 8. This is premature until a proper economic analysis has been done. It may not indeed be true.
   a. We added this comment: «A proper economic analysis is necessary to assess superiority of a method over the other in case of equal effectiveness».

25. P 17, p 5, l 3. Where is inflation for loss to follow up considered?
   a. We did not understand the point of the reviewer. Loss to follow-up was calculated a priori to avoid including in the study too few subjects. We do not need to further correct this.

26. P 17, p 5, l 5. Rewrite as [might well refuse blood sampling and not permit the main …].
   a. Edited as suggested

27. P 18, p 2. Was this a peer review process? If so state it.
   a. We added this statement: «after peer review of the project».

A random sample of 10 Rs was checked for citation accuracy. Two were in need of correction:

28. P 20, R 20, l 1. More to the title: [A Comprehensive Community-Based Approach.].
   a. Edited as suggested.

29. P 23, R 51, l 3. Delete [(Edgmont)].
   a. Done

30. Figure 1. Suggest inserting a break in the horizontal line between 12 and 24 months as the lengths are not correct.
   a. Edited as suggested
31. P 28, Table 3. Suggest noting which have Italian validated scales such as BPRS and WHO QoL.
   a. It is explicitly stated that we used Italian validate versions of the tools.

32. P 29, blinding. Suggest deleting this. See 3.
   a. We disagree with the reviewer. If assessors were more likely to correctly guess groups’ assignment, they could also have biased the evaluation towards the Falloon method, which is allegedly thought to be more effective than other psychoeducation methods. Conversely, if they cannot guess which group patients belonged to, they are unlikely to have biased the evaluation (positively or negatively) towards one method. We thought this is an helpful information.

Reviewer: Sally Chan

1. It would be better if the authors could provide detailed information on the objectives of FPP and GT. From table, 2, it appears that FPP is more focused on problem solving and GT is more focused on information provision. How could the two be compared?
   a. The FPP is based on psychoeducation, which includes the provision of information on the disorder, the offering of support and the training of participants to problem solving. The GT is based on based on a subset of these interventions: emotional support and the provision of information on the disorder. The aim of the comparison is to disentangle specific effects (problem solving) from non-specific effects (those produced by emotional support and the provision of information). The reason is that the training of the therapists to provide problem solving according to the FPP is costly, while therapists are typically able to provide emotional support and information on a disorder.

2. The outcome measures focused on patient outcomes and very few focused on the family members. What are the relationships between the objectives of the programs and the outcome measures?
   a. The study aims at evaluating whether psychoeducation improve the course of schizophrenia because it improves adherence to therapy. Family outcomes will be evaluated about expressed emotion, with the Family Questionnaire, since psychoeducation might modify the family climate and change expressed emotion, which could affect indirectly the main outcome (adherence to therapy).

3. There is a heavy focus on medication adherence in the outcome measures but the interventions are not specifically focus on medication adherence. Could the authors clarify the reason for doing so?
   a. Psychoeducation is expected to improve the course of schizophrenia. In this study we explored the hypothesis that the positive effects of psychoeducation on the course of schizophrenia depends by an indirect effect on medication adherence. In both interventions there is a specific section on medication adherence.

4. There is also measure on expressed emotion but I could not see expressed
emotion in the content of both interventions. Please clarify.

a. As stated before, psychoeducation might modify the family climate and change expressed emotion, which could affect indirectly the main outcome (adherence to therapy). This is the reason we assessed expressed emotion in the study.

5. The study will recruit patients from 10 units. Are the 10 units having similar routine treatment and interventions for patients? How to ensure consistence?

a. The 10 units are not expected to have similar routine treatment. This results in unequal variance by centre. A statistical correction was introduced to deal with this effect. It is customary in multi-centers trials.

6. Who will conduct the interventions and assessment? How to ensure consistence.

a. Interventions and assessment will be conducted by independent staff: those who assess the patients will be not involved in the intervention, and those involved in the intervention will be not involved in the assessment. Both intervention therapist and the assessors received extensive training before the start of the project, and quality assessment will be conducted all over the study to assure that intervention therapists and assessors did not deviate from the instructions they received. In particular, for both the FPP and the GT, the therapists were exposed to two sessions of training with case vignettes and role-playing.