Author's response to reviews

Title: Rationale and design of an independent randomised controlled trial evaluating the effectiveness of aripiprazole or haloperidol in combination with clozapine for treatment-resistant schizophrenia.

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Author’s response to reviews:

Dear Editor,

Many thanks for reviewing the above-mentioned manuscript. We revised it taking into consideration the referees’ comments. Please see below a point-by-point response to the concerns.

I hope the revised version is now suitable for publication in Trials.

Looking forward to hearing from you,

Best wishes,

Michela Nosè

POINT-BY-POINT RESPONSE

1. Will the study design adequately test the hypothesis?
   Yes
   Authors. No revision needed here

2. Are sufficient details provided to allow replication of the work or comparison with related analyses: if not, what is missing?
   • There are no secondary outcomes in this document. More details are required on the other outcomes (secondary) that are listed in the trials registration document (NCT00395915) and on the scales used to measure these, particularly the measure that is not so commonly used (LUNSERS).
   Authors. We reported details on secondary outcomes and on rating scales used to measure psychopathology (Brief Psychiatric Rating Scale, BPRS) and tolerability (Liverpool Side Effect Rating Scale, LUNSERS) (see pag 9).
   • Since this is a multi-centred trial, what measures were used to ensure inter-rater reliability for measurements such as the BPRS and what were the results of any such exercise?
   Authors. In the text we reported that all investigators received training to use the
rating scales. However, no formal inter-rater exercise has been performed (see pag 9)

• Were these measures for psychiatric outcomes (E.g: BPRS) rated by blind assessors?
Authors. Yes, please see page 9.

• The additional file with inclusion and exclusion criteria could replace figure 3 (and tables re-labled so that this is figure 2). I am unsure whether the graph showing recruitment (Figure 3) provides any useful information for this protocol and suggest it is omitted. In place of figure 3, a standard CONSORT flow diagram with actual numbers recruited and dropouts will be more useful (unless this will be reserved for the final report of results).
Authors. We deleted figure 3 as suggested. A CONSORT flow diagram has not been inserted because the three-month follow-up has not been completed yet, so it will be reserved for the final report of results.

3. Is the planned statistical analysis appropriate?
No details on this were provided; a detailed description of the statistical tests that will be used is needed.
Authors. We added a paragraph entitled “Analysis of the primary outcome” to give details on statistical analysis (see pag 12). We have not added information on the analysis of secondary outcomes in order to avoid statistical repetitions, but if the Editor feels it should be added we are ready to do it.

4. Is the writing acceptable?
There are places where the sentence structure needs attention.
Authors. We revised all the text.