Reviewer’s report

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.

Version: 2 Date: 13 March 2009

Reviewer: Prathap Tharyan

Reviewer’s report:

1. Will the study design adequately test the hypothesis?
   Yes

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).

   · 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?

   · Were these measures for psychiatric outcomes (E.g: BPRS) rated by blind assessors?

   · The additional file with inclusion and exclusion criteria could replace figure 3 (and tables re-labeled 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).

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.

4. Is the writing acceptable?

   There are places where the sentence structure needs attention (the trial has finished recruiting so the past tense could be used throughout; some repetition of themes—this is the largest trial on the topic in the western world—could be avoided; and in places, entire sentences need rewording.
Otherwise, this is an excellent study that will provide useful information for clinicians managing people with schizophrenia who are resistant to clozapine.