Reviewer's report

**Title:** Adjunctive Rifampicin to Reduce Early mortality from Staphylococcus aureus bacteraemia (ARREST): study protocol for a multi-centre, randomised, blinded, placebo controlled trial

**Version:** 2 Date: 15 October 2012

**Reviewer:** Rakesh Aggarwal

**Reviewer's report:**

This manuscript describes the design and methodology of a randomized clinical trial which aims to determine whether addition of rifampicin (by oral or intravenous route, versus matched placebo) for a period up to 14 days, to the conventional antibiotic treatment, benefits patients with culture-proven Staphylococcus aureus septicemia, as assessed by reduction in all-cause mortality within 14 days and bacteriological failure or death within 12 weeks from randomization. The trial is multicentric and is pragmatic in nature in that the choice of primary antibiotic will be made by the treating physician.

The protocol is well designed and well written.

The authors do not address the issue of blinding adequately. Rifampicin administration is associated with deep orange colored urine and at times staining of other body fluids. How do the authors propose to blind the study subjects and the study staff.

A few spelling errors need to be corrected, eg. Adjuntive, rifampcicin, etc.

The co-primary endpoints (all-cause mortality through 14 days, bacteriological failure/death through 12 weeks) will be compared using time-to-event methods (Kaplan-Meier plots and logrank tests, Cox proportional hazards regression), as will time to clinical treatment failure/bacteriological failure/death. This may not be appropriate, and comparison of proportions dying in each group may be more relevant. In a study on treatment of an acute infection, the consequences are similar for those who die on day 1, day 14 or week 12 (loss of rest of life), and hence time-to-event analysis would not apply.

The figures included in the file downloaded from the journal URL provided are of low quality. Figures should be of better quality.

The manuscript refers to two ancillary studies within the main trial. One of those is ‘a population pharmacokinetic (PK) and pharmacodynamic (PD) study of rifampicin, flucloxacillin and vancomycin for the treatment of S. aureus bacteraemia’. Would this need the investigators to be unblinded?