Author's response to reviews

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

Authors:

Guy E Thwaites (guy.thwaites@btinternet.com)
Cressida Auckland (cressida.auckland@rdeft.nhs.uk)
Gavin Barlow (gavin.barlow@hey.nhs.uk)
Richard Cunningham (richard.cunningham@nhs.net)
Gerry Davies (gerrydavies@doctors.org.uk)
Jonathan Edgeworth (jonathan.edgeworth@gstt.nhs.uk)
Susan Hopkins (susanhopkins@nhs.net)
Dakshika Jeyaratnam (d.jeyaratnam@nhs.net)
Neil Jenkins (neiljenkins@nhs.net)
Martin Llewelyn (m.j.llewelyn@bsms.ac.uk)
Sarah Meisner (sarahmeisner@nhs.net)
Emmanuel Nsutebu (emmanuel.nsutebu@rlbuht.nhs.uk)
Tim Planche (timothy.planche@nhs.net)
Robert C Read (r.c.read@shef.ac.uk)
Matthew Scarborough (matthew.scarborough@orh.nhs.uk)
Marta Soares (marta.soares@york.ac.uk)
Robert Tilley (robert.tilley@nhs.net)
Estee Torok (estee.totok@addenbrookes.nhs.uk)
John Williams (john.williams@stees.nhs.uk)
Peter Wilson (peter.wilson@uclh.nhs.uk)
Sarah Wyllie (sarah.wyllie@porthosp.nhs.uk)
Sarah Walker (asw@ctu.mrc.ac.uk)

Version: 3 Date: 14 November 2012

Author's response to reviews: see over
Dear Dr Aggarwal,

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

We thank the reviewers for their comments on our manuscript and welcome the opportunity to address them. Our responses are detailed below:

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.

We are slightly puzzled by this comment given the trial’s blinding is addressed at length in the discussion (3 of the 6 paragraphs discuss the issue), and the methods section (‘Treatment of patients’) details how patients and staff will be blinded. Nevertheless, we have added an additional paragraph in the methods section (‘Blinding issues’) which further addresses the issue.
A few spelling errors need to be corrected, eg. Adjunctive, rifampicin, etc.

We have corrected these errors.

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.

We respect the reviewer’s opinion on this matter. However, the hypothesised mechanism of action of rifampicin is through faster killing of S. aureus in the bloodstream: this can be directly assessed through the primary analysis proposed, but not through a logistic regression. Furthermore, the protocol has been approved and the study has started. We do not believe this is sufficiently important an issue to warrant a formal amendment to the protocol. Therefore, we have not revised the analysis plan.

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

We have provided better quality figures, both as PDF and a powerpoint files.

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?

No, the investigators would remain blinded. Samples will be taken without knowledge of randomised allocation, although rifampicin concentrations will only be measured in those receiving active drug. The specimens will be batched and the assays performed in Liverpool after every patient in the batch has completed the trial; the laboratory team performing the assays will only be given the treatment codes for each batch of patients and will perform them without knowledge of the patients’ outcomes. No information about rifampicin levels will be available outside the Liverpool laboratory team before the end of the trial,
although these results would be provided to the trial Data Monitoring Committee. We have clarified this in the text.

Reviewer: Allan Donner

Reviewer’s report:

I have only one comment:

The authors have appropriately adjusted for the two co-primary endpoints in the sample size calculations. However adjustment for this source of multiplicity must also be done in the statistical analysis. Some indication as to how this will be done should be provided.

We have added, ‘All statistical tests of association in the analyses will be interpreted with respect to a 0.025 rather than 0.05 threshold’ after the description of the sample size calculation to clarify this point.

We have moved the ethics statement to the methods, as requested by the editor.

We hope these changes have adequately addressed the editors and reviewers’ comments and the manuscript is now suitable for publication. As included in our original cover letter, we request that all those listed in the acknowledgment section as ‘individual members’ of UKCIRG be linked to the authorship.

Yours Sincerely,

Guy Thwaites

Chief Investigator for the ARREST trial