Author's response to reviews

Title: Modifying Delirium Using Simvastatin (MoDUS): a randomised, double blind, placebo controlled, single centre, phase II clinical trial to evaluate early administration of hydroxymethylglutaryl-CoA reductase inhibitor in the prevention and treatment of delirium in critically ill ventilated patients: study protocol for a randomized controlled trial.

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Author's response to reviews: see over
Dear Editors-in Chief

Please accept our revised manuscript ‘Modifying Delirium Using Simvastatin (MoDUS): a randomised, double blind, placebo controlled, single centre, phase II clinical trial to evaluate early administration of hydroxymethylglutaryl-CoA reductase inhibitor in the prevention and treatment of delirium in critically ill ventilated patients: study protocol for a randomized controlled trial.’ for consideration for publication in Trials.

Thank you very much for the informed and constructive comments from the reviewers regarding our manuscript. In response to referee 2 comments we have revised the manuscript as described below in accordance with the reviewers’ recommendations and we feel our manuscript is considerably improved. We enclose our response for your consideration.

Query

Simvastatin is known to have a short plasma half-life (pharmacokinetics), cytokines are generally rapidly responsive (equating to pharmacodynamics in analogy above) although I accept the effect on different cytokines is variable (e.g. CRP levels change more slowly). If the blood samples for cytokine levels are drawn at a variable part of the day in relation to the administration of simvastatin, how will you be able to differentiate between “a lack of pharmacokinetic/pharmacodynamic persistence +/- concentration variation introduced by staggered timing of sample taking in different subjects” and “no effect”?

Response

Thank you for clarification and apologies for not answering this important point. The blood samples are taken within six hours of drug administration and we have added this detail into the Trial conduct section and research blood section. However as that does not absolutely cover this issue...
we have recently established that it will be feasible to measure simvastatin plasma levels and have
added in “In addition simvastatin plasma levels will be analysed.” We believe this will add to the
credibility of the paper and thank the referee for pursuing this.

Query
A second but related point: RRT is not an exclusion and there are studies that examine removal of
cytokines by this treatment modality. How will you account for the effects on clearance of cytokines
by RRT?

As this is a randomised trial we expect the groups to be balanced in terms of renal dysfunction and
RRT which would account for any differences related to RRT, however in addition we will undertake
the analysis of cytokine levels to look at both the overall cohort and those who are receiving RRT
excluded to address this issue. This will be incorporated into the final statistical analysis plan.

Kind regards

Valerie Page
Chief Investigator