Reviewer's report

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.

Version: 5  Date: 13 January 2015

Reviewer: Mark Borthwick

Reviewer's report:

Many thanks for sharing the revised manuscript which I find interesting and greatly improved.

My comments relate to the secondary outcomes and need answering.

I must return to the issue of cytokine levels and simvastatin effects, I realise I was trying to provide possible answers to my own questions in the previous round and this has confused the issue – apologies for this.

Imagine I suspect that beta blockers might lower someone's blood pressure. I might form a hypothesis that they do this in part by slowing the heart.

If I measured someone's heart rate a few hours after giving some esmolol, I might conclude that the hypotension I noticed a couple of hours ago has nothing to do with bradycardia and some other property is at play. The effect has not persisted long enough for me to detect at my sampling point.

The drug has a short half-life (pharmacokinetics) and its effect is rapidly reversible (pharmacodynamics).

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”?

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?

Level of interest: An article of outstanding merit and interest in its field
Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests