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: 4  Date: 30 October 2014

Reviewer: Mark Borthwick

Reviewer’s report:

1. Thank you for inviting me to review this manuscript, it is an honour to be so asked.

2. The study hypothesis is very interesting: does the prophylactic administration of simvastatin to ventilated critically ill patients increase the number of delirium-free days up to day 14 of admission, does simvastatin have an effect seen in a raft of further investigations to measure biomarkers, anticholinergic activity and beta-amyloid measured from plasma, and finally does simvastatin (short term administration) change any effects of delirium on longer term cognitive outcomes.

3. Given the possible mechanisms of action of statins in moderating inflammation against the worries about the adverse effects of statins on cognition (even knowing the jury is still out on the latter) there are certainly some very good questions to be answered here.

4. The proposed clinical outcome measures are pragmatic for a phase 2 study. The numerous biological tests seem appropriate, on the one hand there is no doubt others could be added but on other there already numerous measures increasing the possibility of a type II error – this will need to borne in mind when the results are available.

5. Eligibility criteria are pragmatic. With respect to exclusion criteria, the safety aspect of high dose simvastatin treatment has been well controlled. The 80mg dose would have worried me when the study started had these measures not been put in place, although I am also more relaxed now because of the very reassuring safety data arising from the HARP-2 study.

6. There is not enough information provided in the sample size calculation to determine whether the sample size has been calculated correctly or if the size of the effect being looked for is clinically relevant. It should be a simple task to add the relevant information in - the manuscript should not be published without it.

7. The trial conduct description overall is very rigorous. I have only two points for clarification in a very well thought out set of trial protocols.
8. I am aware that crushed tablets (for NG administration) have varying colour and dissolution properties when mixed with water. A line in the manuscript to assure readers that the placebo and active tablets are indistinguishable when crushed and dispersed in water for NG administration as well as when whole would be welcomed as this is important for the blinding aspect.

9. It is clear that study drug will be administered at a specific time of day (10am). It is not clear what the timing window for drawing specimens for the various biological assays is. The half-life of simvastatin is very short, approximately 2 hours though this is likely lengthened in critical illness. The pharmacodynamics of simvastatin in critical illness are even less well described. Any effect on the biomarkers studied will be consequent on the concentration of simvastatin in the target tissues and this is likely to be related to the plasma simvastatin level. Given the short half-life, it is probable that plasma simvastatin levels change from maximal concentration to near nothing over the course of a single day, and this may affect any interaction with inflammatory mediators, etc, evidenced by changes in plasma concentrations of those mediators/ anticholinergic activity/ beta amyloid.

This could be controlled for by doing simultaneous simvastatin levels, or by drawing blood samples for the biomarker studies within a reasonable time window in relation to when the dose is administered, e.g. 3-6 hours post dose. There may of course be pharmacokinetic or pharmacodynamic data from other studies that indicates this is not necessary, and if this is so, this should be cited.

10. The overall statistical plan seems fine though it has not yet been fully developed. A 5% significance level is reasonable given the small scale nature of this study, although a Bonferroni correction may be required. The health economic analysis is standard, and fairly ambitious for a 164 patient study.

11. I really like the inclusion of ICUsteps (patients) on the trials steering committee.

12. The discussion section is not particularly long, but does the job. I would take out the word “brain” in the final paragraph of the discussion. Statins may very well have an effect on inflammatory pathways in the brain itself, but this study looking at peripheral levels of biological mediators would not be able to say one way or the other.

Major revisions 8, 9
Minor revisions 6
Discretionary revisions 4, 10, 12

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the
statistics.

Declaration of competing interests:

I declare I have no competing interests