Author's response to reviews

Title: Hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in Acute lung injury to Reduce Pulmonary dysfunction (HARP-2) trial protocol: A randomised, double-blind, placebo controlled trial of simvastatin in acute lung injury.

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Please accept our revised manuscript (MS: 1526480406702408) entitled "Hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in Acute lung injury to Reduce Pulmonary dysfunction (HARP-2) trial protocol: A randomised, double-blind, placebo controlled trial of simvastatin in acute lung injury." for re-consideration for publication in Trials.

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

As requested we have ensured that our revised manuscript conforms to the journal requirements. We have also tracked changes as requested. In addition to addressing the reviewer’s comments in the revised manuscript, we have added the institution for Gavin Perkins on the title page, which was omitted accidently in the initial version and have updated the funding statement.

Reviewer: 1  
We are grateful for the supportive comments.

C1 The authors may wish to consider adding a reference to the ongoing Phase III trial of rosvastatin for infection-related lung injury being conducted in the US by the NHLBI’s ARDS network.
R1 This has been added. I have also added that the NHLBI’s ARDS network is investigating rosvastatin in infection-related ALI only while in contrast HARP-2 trial is recruiting patients with ALI irrespective of aetiology to highlight one of the main differences between the trials.

C2 How frequently will safety labs be monitored? I presume they will be checked at each of the blood draws referenced on the bottom of page 7, but clarification
may be helpful.

R2 Safety monitoring (CK and liver transaminases) is undertaken at days 3, 7, 14, 21 and 28. This has been clarified in the manuscript.

Reviewer: 2
Again we are grateful for the supportive comments.

C3 The authors have adopted a robust study design to optimise the success of the study and to address their specified hypothesis – a multicentre, prospective, randomised, allocation concealed, double-blind, placebo-controlled clinical trial of simvastatin treatment to improve clinical outcomes (primary outcome is VFD-28) in patients with acute lung injury. There is extensive detail on all aspects of trial conduct detailing their management e.g. unblinding process of deemed necessary, feedback to data monitoring committee. Furthermore the trial is registered with all appropriate governing bodies, and it is stated that trial conduct will follow established practice guidelines in terms of day-to-day operation and ultimate reporting of data.

R3 Thank you for this comment.

C4 Primary outcome for the study (ventilator free days, VFD-28) is clearly defined, and secondary outcomes are clear. There is detail on the reporting of adverse events that may occur. Eligibility criteria are clearly stated and additional detail regarding post randomisation withdrawals and exclusions. Minor point: #12 of the exclusion criteria (Page 9) needs to be clarified further for this reviewer ‘Domiciliary Mechanical Ventilation’ is ‘BIPAP’ and this can be used for management of Sleep-Disordered Breathing. Are all patients receiving Home Mechanical Ventilation (a more useful term) excluded?

R4 If the patient is receiving mechanical ventilation other than ventilatory support solely for sleep-disordered breathing then the patient is excluded. This is in line with the definition used in previous multi-centre ARDSnet studies and the ongoing National Heart, Lung, and Blood Institute ARDS network trial of rosuvastatin for infection-related ALI (SAILS study; NCT00979121).

C5 The authors report that ‘patients receiving pressure support with non-invasive ventilation will be defined as receiving assisted ventilation’ (Page 6). If patients with Sleep-Disordered Breathing on CPAP/BIPAP are included in the trial, the investigators may want to reconsider this definition. A suggestion is that nocturnal CPAP/BIPAP in those on pre-existing CPAP/BIPAP will not be defined as received assisted ventilation. This reviewer acknowledges that this is a very small proportion of the 524.

R5 The reviewer is correct and we acknowledge this has potential to cause confusion. In fact what the reviewer suggests is the actual operational study definition of unassisted ventilation used in the study currently which allows the use of usual CPAP or BIPAP solely for sleep-disordered breathing management. Any additional support (pressures or period of time) above the usual level of ventilatory support for sleep-disordered breathing management or non-invasive
ventilation for any other reason is defined as assisted breathing. This has been clarified in the manuscript.

C6 In ‘Power and sample size estimate’, paragraph 1, the authors report data from ARDS Network study of mean (SD) for VFDs. They go on to state that the SD used for the current protocol is similar to that consistently reported in the literature, and refer to three other studies. Minor point: Is the SD used for the current study protocol similar the ARDS Network study? R6 Yes; the SD used for the sample size estimate was the SD from the ARDS Network study, ie 10.6. This has been clarified in the manuscript.

C7 Minimisation is by (1) site and (2) vasopressor requirement. Minor Point: Is there a requirement to minimise by intra-pulmonary or extrapulmonary causes of ALI? Does this effect outcome? This reviewer is mindful of the H1N1 pneumonitis/ALI that was a major health issue during Winter 2010/2011. R7 We decided not to stratify on the basis of pulmonary or extra-pulmonary causes of ALI as there is often an overlap as to whether a patient has a pulmonary or extra-pulmonary cause for their ALI and the data that this determines outcome is contradictory.

C8 The authors report that recruitment will take place across approximately 35 ICUs across UK and Ireland. Could the authors indicate how long they anticipate recruitment to take, based on their sample size? Cessation of trial funding is stated as one potential causal factor for ending the trial. What is the risk of this depending on anticipated recruitment rates and duration of current funding? R8 This is an important point. Recruitment was below the planned accrual target initially. However we have made significant efforts to improve recruitment and these measures have substantially increased recruitment. In the past 9 months we have averaged 15-16 patients per month, and in the past 5 months we have averaged 20 patients per month. Going forward we have therefore estimated a conservative recruitment rate of 15 patients per month and are confident this can be achieved on the basis of the current actual recruitment rate. In confidence (pending contractual agreement), the NIHR EME programme have agreed an extension for the trial which will allow recruitment to continue for an additional 12 months to May 2014 and therefore the risk of cessation of trial funding ending the trial is now very low.

C9 There is a secondary end-point of ‘Biological Mechanisms’. Is blood/urine to be analysed at a single centre? R9 Yes, blood and urine are stored, and will be analysed, at a single centre (Queen’s University Belfast).

C10 The eligibility criteria requires radiological assessment to diagnose ‘bilateral infiltrates on CXT consistent with pulmonary oedema’. Will this be reported by the local PI and their team? Will it be subsequently be reported by a radiologist? This will provide interesting data separate from the main trial.
R10 The CXR will be reported by the local ICU team and it is not a requirement for the study that it is subsequently be reported by a radiologist. However as suggested by the reviewer, we acknowledge this would provide interesting data and pending funding, we will consider this additional question.

C11 Minor Essential Revisions
R11 These have all been made as requested.

All authors agree with submission of this paper. The work is not being considered for publication elsewhere.

We look forward to hearing from you.

Yours faithfully,

Danny McAuley