Reviewer's report

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.

Version: 2 Date: 17 July 2012

Reviewer: Nicholas Hart

Reviewer's report:

Overall Comment
The authors present a complete and comprehensive trial protocol building on previous proof of concept data, and now powered to detect the effect on clinical outcomes, of treatment with Simvastatin (Hydroxymethylglutaryl-CoA Reductase Inhibitor) in patients with acute lung injury (ALI). The protocol is clearly written, the primary and secondary end-points are clearly defined and presented in a logical manner. Furthermore, there is a secondary endpoint to understand the possible biological mechanism. It is evident that attention to detail has been paid to all aspects of trial design to ensure credibility and robustness and therefore it is not surprising that this trial has received prestigious NIHR HTA funding. There is in depth background justification for the hypothesis relating to data other than the authors' original work and detailed method and intended analysis provided. This reviewer agrees that minimisation by site is essential as each site will use ‘best practice established locally’ in the management of ALI and therefore these needs to be accommodated into the trial design to ensure there is no centre effect. There is detailed description of the drug administration including the blinding process and the processes to ensure blinding is maintained. In addition, the authors have provided a section on ‘unblinding’. Finally, all the standard organisational structure, organisations and agencies, such TSC, Ethics, R&D, MHRA, CTU, Independent DMEC, have been outlined including statistical and health economics analysis.

Major comments/revisions
1. 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.
2. 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?

3. 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.

4. 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?

5. 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.

6. 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?

7. There is a secondary end-point of ‘Biological Mechanisms’. Is blood/urine to be analysed at a single centre?

8. 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 is be subsequently be reported by a radiologist? This will provide interesting data separate from the main trial.

Minor Essential Revisions
1. Abstract – Line 3; Change ‘There is in vitro..........data’ to ‘There are ..........data’.
2. Background – Line 3; remove ‘Bernard’ from sentence (refers to author of reference 1)
3. Background – Line 4; include ‘and’ in ‘.....ratio of < 40kPa), and bilateral infiltrates....’
4. Rationale for statins in the treatment of ALI – Line 9; remove ‘in healthy
volunteers’ (duplicated from the beginning of the sentence)

5. A single centre, randomised double-blind, placebo-controlled study – Line 1; remove open bracket in from before ‘Hydroxymethylglutaryl....’ and move to before HARP on Line 2 (which is the abbreviation)

6. A single centre, randomised double-blind, placebo-controlled study – Line 11; change ‘...was...' to 'is'

7. A single centre, randomised double-blind, placebo-controlled study – Line 12; change ‘...was...' to 'is'

8. Methods/Design – Line 15; remove ‘...The trial....’ and replace with ‘...and...’ to avoid repetition of ‘The trial will’

9. Biological mechanisms – Line 3; add ‘the’ in ‘...to receive the study drug...’

**Level of interest:** An exceptional article

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

Ans. No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

Ans. No

Do you hold or are you currently applying for any patents relating to the content of the manuscript?

Ans. No

Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

Ans. No

Do you have any other financial competing interests?

Ans. No

Do you have any non-financial competing interests in relation to this paper?
Ans. No

I declare that I have no competing interests' below.