HARP-2

*H*ydroxymethylglutaryl-CoA reductase inhibition with simvastatin in *A*cute lung injury to *R*educe *P*ulmonary dysfunction

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STATISTICAL ANALYSIS PLAN

Version 3.0 [final]

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This document and all preceding versions will be stored in the Trial Master File for this trial

Contents

1. BACKGROUND AND DESIGN

The aim of this trial is to test the hypothesis that treatment with enteral simvastatin 80mg once daily for a maximum of 28 days will be of therapeutic value in patients with acute lung injury (ALI). The study has two distinct objectives:

Objective 1: To conduct a prospective randomised, double-blind, placebo-controlled phase II multi-centre trial of simvastatin for the treatment of ALI.

Objective 2: To study the biological effect of simvastatin treatment on: (2a) systemic markers of inflammation; (2b) systemic cell-specific indices of activation and injury to the alveolar epithelium and endothelium; (2c) lung extracellular matrix degradation; (2d) assess whether response to simvastatin is determined by genetic polymorphisms as well as link genotypic information to the phenotypic information recorded as part of this study.

The trial interventions will be simvastatin 80mg once daily (as two 40mg tablets) or 2 identical placebo tablets administered enterally via a feeding tube or orally for up to 28 days. Randomisation will be stratified by site and by vasopressor requirement (defined as any inotropic requirement except dopamine < 6mcg/kg/min).

The Primary Outcome Measure will be ventilator free days (VFDs) and the Secondary Outcome Measures are (a) Change in oxygenation index (OI) from baseline to day, 3, 7, 14 and 28; (b) Change in sequential organ failure assessment (SOFA) score from baseline to day 3, 7, 14 and 28; (c) non pulmonary organ failure free days (OFFD); (d) All cause mortality 28 days post randomisation; (e) Mortality at (first) discharge from critical care; (f) Mortality at (first) discharge from acute hospital; (g) Mortality at 12 months post randomisation; (h) Safety; (i) Biological mechanisms; (j) Health-related quality of life; (k) Cost effectiveness.

Patients will be eligible to participate in the study if they fulfil the following inclusion and exclusion criteria.

Inclusion criteria:

1. Patient must be receiving invasive mechanical ventilation
2. Patient must have ALI [34] as defined by acute onset of:

a) hypoxic respiratory failure ($PaO^2/FiO^2 \leq 40$ kPa from 2 blood gases >1 hour apart).
b) bilateral infiltrates on chest X-ray consistent with pulmonary oedema.
c) No clinical evidence of left atrial hypertension or if measured, a pulmonary arterial occlusion pressure (PAOP) less than or equal to 18 mmHg. If a patient has a PAOP > 18 mmHg, then the other criteria must persist for more than 12 hours after the PAOP has declined to < 18 mmHg, and still be within the 48-hour enrolment window

Acute onset is defined as follows: the duration of the hypoxia criterion (a) and the chest X-ray criterion (b) must be <28 days at the time of randomisation.

Infiltrates considered "consistent with pulmonary oedema" include any patchy or diffuse infiltrates not fully explained by mass, atelectasis, or effusion or opacities known to be chronic (>28 days). The findings of vascular redistribution, indistinct vessels, and indistinct cardiac borders are not considered "consistent with pulmonary oedema".

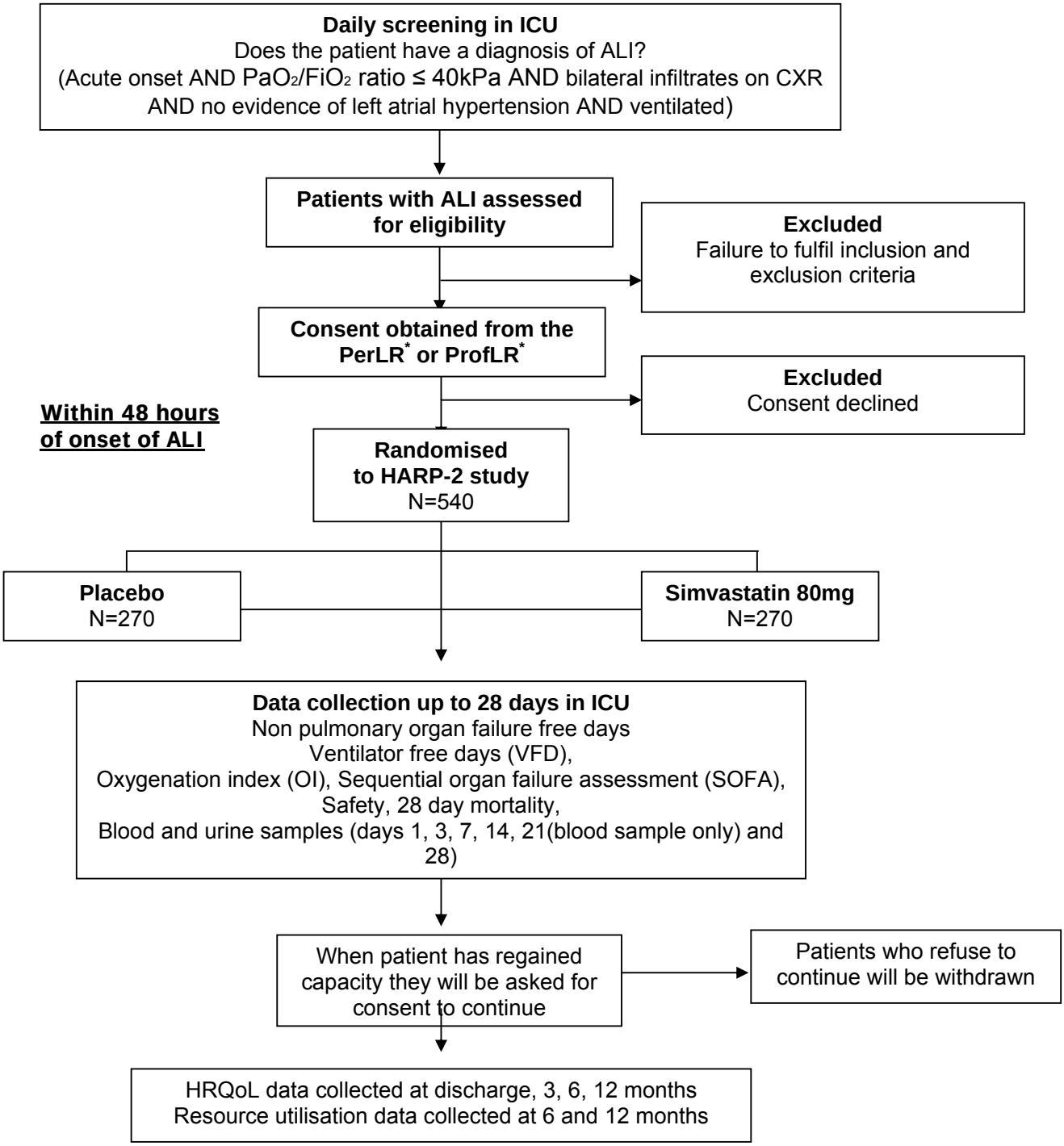
All ALI criteria (a-c above) must occur within the same 24-hour period. The time of onset of ALI is when the last ALI criterion is met. Patients must be enrolled within 48 hours of ALI onset

Exclusion criteria:

1. Age < 16 years
2. More than 48 hours from the onset of ALI
3. Patient is known to be pregnant
4. CK >10 times the upper limit of the normal range*
5. Transaminases >8 times the upper limit of the normal range*
6. Patients currently receiving ongoing and sustained treatment with any of the following; itraconazole, ketoconazole, HIV protease inhibitors, nefazodone, cyclosporine, amiodarone, verapamil or diltiazem
7. Patients with severe renal impairment (calculated creatinine clearance less than 30ml/minute) not receiving renal replacement therapy
8. Severe liver disease (Child's Pugh score >12; Appendix 1)
9. Current or recent treatment (within 2 weeks) with statins
10. Physician decision that a statin is required for proven indication
11. Contraindication to enteral drug administration, e.g. patients with mechanical bowel obstruction. Patients with high gastric aspirates due to an ileus are not excluded.
12. Domiciliary mechanical ventilation except for CPAP/BIPAP used for sleep-disordered breathing
13. Known participation in other investigational medicinal product (IMP) trials within 30 days
14. Consent declined
15. Treatment withdrawal imminent within 24 hours
16. Non-English speaking patients or those who do not adequately understand verbal or written information unless an interpreter is available

* If CK, ALT and AST values are not available as part of routine care, a blood sample will be obtained after informed consent but before randomisation. CK, ALT and AST values may be obtained up to 72 hours prior to randomisation.
Day 1 bloods are the baseline bloods and therefore are those bloods used to determine eligibility.

Trial Schematic Diagram



*PerLR – Personal Legal Representative
*ProfLR – Professional Legal Representative

Full details of the background to the trial and its design are presented in the protocol.

2. OUTCOME MEASURES

2.1 Primary outcome measure

The primary outcome measure is VFDs to day 28 defined as the number of days from the time of initiating unassisted breathing, to day 28 after randomisation.

VFDs to day 28 are defined as the number of days from the time of initiating unassisted breathing to day 28 after randomisation, assuming survival for at least two consecutive calendar days after initiating unassisted breathing and continued unassisted breathing to day 28. If a patient returns to assisted breathing and subsequently achieves unassisted breathing to day 28, VFDs will be counted from the end of the last period of assisted breathing to day 28. A period of assisted breathing lasting less than 24 hours and for the purpose of a surgical procedure will not count against the VFD calculation. If a patient was receiving assisted breathing at day 27 or dies prior to day 28, VFDs will be zero. Patients transferred to another hospital or other health care facility will be followed to day 28 to assess this endpoint.

2.2 Secondary outcome measures

There are a number of secondary outcomes for this clinical trial which include clinical outcomes, safety, biological mechanisms and data for the economic evaluation. The primary analysis will report on all short term clinical and safety outcomes.

A secondary analysis will be undertaken following collection of long term outcomes such as 12 month mortality, economic evaluation data and analysis of all biological mechanism data is completed and will be reported separately.

Clinical Outcomes

1. Change in oxygenation index (OI) from baseline to day 3, 7, 14 and 28
2. Change in sequential organ failure assessment (SOFA) score from baselines to day 3, 7, 14 and 28
3. Non pulmonary organ failure free days, (defined as the number of days in the first 28 days after randomisation that the patient has none of: cardiovascular support, renal support, liver support or neurological support).
4. All cause mortality 28 days post randomisation
5. Mortality at (first) discharge from critical care
6. Mortality at (first) discharge from acute hospital
7. Mortality at 12 months post randomisation

Note: Clinical outcomes 1-3 are while data is collectable in ICU

Safety

1. CK >10 times the upper limit of normal (measured on days 1, 3, 7, 14, 21 and 28)
2. ALT/AST >8 times the upper limit of normal (measured on days 1, 3, 7, 14, 21 and 28)
3. Need for renal replacement therapy in patients with CK elevated >10 fold
4. Serious adverse events (SAEs) and occurrence of suspected unexpected serious adverse reactions (SUSARs) as defined in section 7.4.2 of the protocol

Note: Safety outcomes 1-3 are while receiving study drug

Biological mechanisms

1. Neutrophil activation biomarkers which may include but are not limited to measurement of plasma MPO and MMP-8
2. Plasma inflammatory response biomarkers which may include but are not limited to measurement of CRP, cytokines (including but not limited to TNFα, IL-1β, IL-6, IL-8), proteases and anti-proteases, HO-1, adhesion and activation molecule expression (including but not limited to sICAM-1), coagulation factors (including but not limited to

thrombin-anti-thrombin complex, tissue factor, protein C, thrombomodulin and plasminogen activator inhibitor-1), RAGE ligands and vitamin D status

3. Alveolar epithelial and endothelial injury biomarkers which may include but are not limited to measurement of plasma cell specific biomarkers such as RAGE, SP-D, Ang I/II and vWF)
4. Systemic endothelial function biomarkers which may include but is not limited to measurement of spot urine albumin:creatinine ratio (ACR)
5. Pulmonary extracellular matrix (ECM) degradation and turnover biomarkers which may include but are not limited to measurement of urinary desmosine indexed to urine creatinine and procollagen peptide III
6. Assess whether response to simvastatin is determined by genetic polymorphisms as well as link genotypic information to the phenotypic information recorded as part of this study
7. Peripheral blood NF-κB activation

Data for Economic Evaluation

1. Health related quality of life (HRQoL)
   EQ-5D at discharge 3, 6 and 12 months post randomisation
2. Resource use:
   Length of ICU stay (level 3 care)
   Length of HDU stay (level 2 care)
   Length of acute hospital stay
   Health service contacts up to 12 months post randomisation

3. DATA

3.1 CRF Forms and variables

Full details of data collection and timing are described in the trial protocol.
A copy of the CRF and Quality of Life (QL) questionnaires are present in the Trial Master File.

3.2 Management of datasets

At the time of analysis:

The Data Manager in collaboration with the Trial Statistician will extract data from MACRO, the clinical trial database, following procedures as detailed in the SOP DM09 Database Closure and the corresponding study Data Management Plan.

3.3 Data completion schedule

The following table describes the time points for completion of clinical record forms and quality of life questionnaires.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8-28	Day 14	Day 21	Day 28	Discharge and 3 months	6 and 12 months
Eligibility assessment	X												
Informed consent	X												
Baseline evaluation and demographics	X												
Randomisation	X												
Study drug administration	X	X	X	X	X	X	X	X					
Ventilation status	X	X	X	X	X	X	X	X					
Oxygenation index (OI) Sequential Organ Failure Assessment (SOFA)	X		X				X		X		X		
Blood sampling (safety)	X		X				X		X	X	X		
Blood and urine sampling (mechanisms)	X		X				X		X		X		
Adverse events	X	X	X	X	X	X	X	X					
Survival status	X	X	X	X	X	X	X	X				X	X
HRQoL assessment (EQ-5D)												X	X
Resource utilisation data													X

3.4 Data verification

The process of data verification ensuring and quality of the data will be carried out according to the SOPs DM04 Data Validation and Discrepancy Management and QM02 Quality Control Procedures – Data Management. The corresponding study Data Management Plan also gives details on the percentage of data to be reviewed, what the critical fields are and the timing of the Quality Control checks.

3.5 Data coding

The variable codings will be as specified on the CRF.

4. DEFINITION OF TERMS

Term	Definition
Ventilator Free Days (VFDs)	VFDs to day 28 are defined as the number of days from the time of initiating unassisted breathing to day 28 after randomisation, assuming survival for at least two consecutive calendar days after initiating unassisted breathing and continued unassisted breathing to day 28. If a patient returns to assisted breathing and subsequently achieves unassisted breathing to day 28, VFDs will be counted from the end of the last period of assisted breathing to day 28. A period of assisted breathing lasting less than 24 hours and for the purpose of a surgical procedure will not count against the VFD calculation. If a patient was receiving assisted breathing at day 27 or dies prior to day 28, VFDs will be zero. Patients transferred to another acute hospital or other health care facility will be followed to day 28 to assess this endpoint.
Non pulmonary Organ Failure-Free Days (OFFDs)	Number of days in the first 28 days after randomisation that the patient has none of: cardiovascular support, renal support, liver support or neurological support. If a patient dies prior to day 28, OFFDs will be zero.
Oxygenation Index	$\frac{\text{Mean Airway Pressure } (cmH_2O)}{PaO_2(kPa)/FiO_2 \text{ Ratio}}$
Ideal Body Weight (IBW)	Males: IBW (kg) = 50 + 0.91x(height (cm) - 152.4). Females: IBW (kg) = 45.5 + 0.91x(height (cm) - 152.4)
Tidal Volume (TV) (per kg Ideal Body Weight)	TV/IBW

5. SAMPLE SIZE CALCULATIONS

The mean (standard deviation; SD) VFDs in 432 patients with ALI was 12.7 (10.6) days.

There are no prospective trials in patients with ALI to predict the treatment effect size of simvastatin to improve VFDs. In a recent retrospective study, statin usage in patients with ALI was associated with a 31% increase in VFDs. Our observational data showed a 37% relative improvement in ICU mortality in patients who received a statin. In our proof of concept study OI and SOFA score improved by 50-66% respectively in the simvastatin-treated group. Pre-treatment with simvastatin decreased a range of pulmonary inflammatory mediators induced by lipopolysaccharide in healthy volunteers by between 34-65%. On the basis of these data, a conservative treatment effect of 20% has been estimated for this study.

A 20% treatment effect represents a 2.6 day increase in VFDs. A 2.6 day increase in VFDs either as a result of improved mortality and/or decreased duration of ventilation would be of major importance from a clinical, patient based and resource point of view. Previous studies have found that interventions can demonstrate a change in VFDs of a similar or greater magnitude. In a study comparing liberal and restrictive fluid regimens in ALI a similar difference in VFDs was seen. In addition in a study of 2 different ventilatory strategies a reduction of 4 VFDs was achieved. This indicates that a treatment effect size of 2.6 VFDs can be achieved.

A sample size of 524 subjects (262 in each group) will have 80% power at a two-tailed significance level of 0.05 to detect a 20% difference in VFDs. To estimate loss after recruitment, previous data from the PAC-Man trial were used where 2.4% of recruited patients or their relatives subsequently withdrew their consent, or were randomised in error. Thus if a dropout rate of 3% is estimated this study will require a total of 540 patients (270 in each group).

The SD (10.6) for VFDs in ALI used for the sample size calculations is similar to the SD for VFDs that has been consistently reported in other large multi-centre clinical trials. In our proof of concept study the SD for VFDs was smaller at 8.7 days in the placebo group, albeit this was a single centre study. If a similar SD was found in the proposed clinical trial then our estimated power would be greater.

Via the DMEC, when the primary outcome measure of VFDs is available for 270 patients, a sample size review will be undertaken by the independent statistician. The purpose of this will be to check that the within-groups variance has not been substantially underestimated which would mean that the sample size had been underestimated. No other data will be analyzed. The group allocation of the patients will not be revealed and this review would not compare the two groups to examine treatment effects. In keeping with recommendations on interim sample size review, the review would not lead to a reduction of the sample size. The review would either lead to a recommendation that the sample size remains unchanged or that it should be increased. The DMEC would consider whether a recommended sample size increase is feasible.

6. ANALYSIS PRINCIPLES

Analyses will be on an intention-to-treat basis and all statistical tests will be at the 2-sided p-value of 0.05 unless adjustment for multiple testing is needed. As VFDs and OFFDs are likely to have a bimodal distribution, the groups will initially be analyzed by t-test with difference in means and 95% confidence intervals (CI) presented. A secondary analysis of these outcome measures involving a bootstrapped t-test will also be conducted to support the findings of the t-tests. The comparison of other continuous outcomes will be by analysis of variance, including covariates where appropriate. Statistical diagnostic methods will be used to check for violations of the assumptions, and transformations will be performed where required. A statistical interaction test will be used to assess differences in treatment effects between the subgroups. For binary outcome measures, risk ratios and associated 95% CI will be calculated. Binary variables assessed daily will be analysed using logistic regression analysis corrected for days at risk. Time-to-event data will be presented using Kaplan-Meier plots. In all time-to-event analyses, patients that have not experienced the event in question (e.g. death) will be censored on the date last seen or 60 days. Time-to-event data will be tested using a log-rank χ^2 test. The number of events observed and the log-rank expected number of events will be presented. Log-rank hazard ratios (HRs) will be calculated to test the difference between the treatment arms as these methods make no assumptions about

proportionality of the hazards on each arm. All HRs will be presented with a 2-sided 95% CI. Median follow-up time will be calculated.
Correlations between changes in the biological markers measured and physiological and clinical outcomes will assessed by appropriate graphical and statistical methods including χ^2 and Pearson's correlation coefficient.

Subgroup analyses will use a statistical test for interaction and will be reported using 99% CI.

Four subgroup analyses are pre-specified, stratifying by:
1. Age in quartiles
2. Vasopressor requirement (defined as any inotropic requirement except dopamine < 6mcg/kg/min) as presence or absence
3. Sepsis versus non-sepsis aetiology
4. CRP level at baseline in quartiles

To assess whether any treatment is more or less effective in well-defined subgroups, $\chi 2$ tests for heterogeneity or, where appropriate, trend analysis will be performed. Forest plots will be presented to visually summarize the consistency of an effect over the subgroups.

Important time points for clinical outcomes such as change from baseline (day 1) in OI and SOFA are days 3, 7, 14 and 28, while data collectable in ICU. Important time points for CK >10 and ALT/AST >8 times the upper limit of normal are days 1, 3, 7, 14, 21 and 28 while patient receiving study drug.

Every effort will be made to minimise missing baseline and outcome data in this trial. The level and pattern of the missing data in the baseline variables and outcomes will be established by forming appropriate tables and the likely causes of any missingness will be investigated. This information will be used to determine whether the level and type of missing data has the potential to introduce bias into the analysis results for the proposed statistical methods, or substantially reduce the precision of estimates related to treatment effects. If necessary, these issues will be dealt with using multiple imputation or Bayesian methods for missing data as appropriate.

A within-trial Cost Effectiveness Analysis (CEA) will be undertaken to compare the costs and outcomes of patients in each arm of the trial at 12 months follow-up (post-randomisation). A health service perspective will be adopted for this analysis as recommended by the National Institute for Health and Clinical Excellence (NICE) with additional information being collected relating to social care costs. The outcome for the analysis will be the Quality Adjusted Life Year (QALY) and utilities will be measured using the EQ-5D at discharge, 3, 6 and 12 months. Resource utilisation will be collected at 6 and 12 months only. Administration of the EQ-5D (at 4 separate time points) has been undertaken to ensure that any utility differences between arms will be fully captured.

Consistent with the perspective chosen for the analysis, resource utilisation will be quantified (at all sites to allow evaluation of cost-effectiveness in both jurisdictions), however, the focus of the proposed evaluation will be to determine cost-effectiveness within a UK context. Hence unit costs will be applied from national sources such as the National Health Service (NHS) reference costs, British National Formulary (BNF) and the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care. Where national costs are not available, unit costs will be identified in consultation with finance departments of hospitals/Trusts. Patient-specific resource utilisation (of primary, community and social care services) will be extracted from the trial CRF and via self-completed patient questionnaires. It will not be

necessary to discount costs and outcomes (for the within-trial analysis) given the duration of follow-up.

UK population norms for the EQ-5D will be used to assign utility scores to participants' health states at specific time points. By using area-under-the-curve methods which effectively multiplies utility by time, patient-specific QALYs accrued over the 12 month period will be estimated.

The incremental cost-effectiveness ratio (ICER) will be calculated as the difference in the mean costs divided by the difference in the mean QALYs gained between groups. Multiple regression models will be used to predict costs and effects adjusted for covariates. Uncertainty in the point estimate of the ICER will be investigated by means of non-parametric bootstrapping with 1,000 replications. The resulting 1,000 ICER replicates will be plotted on the cost-effectiveness plane and used to construct a cost-effectiveness acceptability curve (CEAC). This curve indicates the probability of the intervention being more cost-effective than usual care for a range of potential maximum amounts of money the decision maker would be willing to pay per QALY. The results of the cost-effectiveness analysis will also be summarized by calculating the net monetary benefit (NMB) of the intervention. The difference in QALYs gained between groups will be re-scaled into monetary value using the threshold willingness-to-pay per QALY and then subtracting the difference in costs from this value. The results will be presented diagrammatically. Sensitivity analysis will be performed to assess the robustness of the cost-effectiveness analysis to changes in key parameters. This will include testing the sensitivity of the estimates to model specifications by re-estimating the multiple regression models and exploring different methods of dealing with missing data.

7. ANALYSIS DETAILS

The results of the analyses will be reported following the principle of the ICH E3 guidelines on the Structure and Content of Clinical Study Reports.

7.1 Recruitment and follow-up patterns

- Recruitment by year, centre
- The number of withdrawals by treatment group

7.2 Baseline Characteristics

The randomisation is stratified by site and vasopressor requirement.

- Gender, number no. (%) by treatment arm
- Sepsis or Non Sepsis, no. (%) by treatment arm
- Vasopressor Requirement, no. (%) by treatment arm
- Plateau Pressure, mean (SD) by treatment arm
- ALI aetiology, no. (%) by treatment arm
- Age at randomisation, mean (SD) by treatment arm
- PaO_2/FiO_2 ratio at randomisation, mean (SD) by treatment arm
- Apache II score, mean (SD) by treatment arm
- SOFA score, mean (SD) by treatment arm
- Oxygenation Index, mean (SD) by treatment arm

- Tidal Volume (per kg Ideal Bodyweight), mean (SD) by treatment arm
- Lowest Mean Arterial Pressure, mean (SD) by treatment arm

7.3 Trial treatment

- Study drug given no (%)
- Treatment compliance/tolerance including reasons for early discontinuation or protocol violations, no (%) by treatment arm
- Frequency and reason for dose modification and delays by treatment arm
- Non trial statin administered, no (%) by treatment arm

7.4 Trial events

- VFDs to day 28, mean [SD] by treatment arm and difference in mean with 95% CI
- OFFDs, mean [SD] by treatment arm difference in mean with 95% CI
- Change in oxygenation index (OI) from baseline to day 3, 7, 14 and 28, mean (SD) by treatment arm
- Change in sequential organ failure assessment (SOFA) score from baselines to day 3, 7, 14 and 28, mean (SD) by treatment arm
- All cause mortality 28 days post randomisation, no. (%) by treatment arm
- Mortality at (first) discharge from critical care/ discharge from hospital / 12 months post randomisation, no. (%) by treatment arm
- CK >10 times the upper limit of normal (measured on days 1, 3, 7, 14, 21 and 28), no. (%) by treatment arm
- ALT/AST >8 times the upper limit of normal (measured on days 1, 3, 7, 14, 21 and 28), no. (%) by treatment arm
- Need for receipt of renal replacement therapy in patients with CK elevated >10 fold, no. (%) by treatment arm not receiving renal replacement therapy at randomisation
- Biological Mechanisms

Four subgroup analyses are pre-specified, stratifying by:

1. Age by quartiles
2. Vasopressor requirement (defined as any inotropic requirement except dopamine < 6mcg/kg/min); presence or absence
3. Sepsis versus non-sepsis aetiology of ALI
4. CRP level at baseline by quartiles

7.5 Toxicity/ Symptoms

- Serious adverse events (SAEs) and occurrence of suspected unexpected serious adverse reactions (SUSARs), no. (%) by treatment arm
- Adverse reactions (ARs) including increases in CK, ALT and AST as described in section 7.4
- Serious adverse reactions including need for renal replacement therapy as defined in section 7.4.
- Adverse events (AEs)

7.6 Quality of life and Healthcare Resource Use

- EQ-5D scores at discharge 3, 6 and 12 months post randomisation, mean (SD) by treatment group

- Quality-adjusted life years (QALYs) gained at 12 months post randomisation, mean (SD).
- Length of ICU stay (level 3 care) / HDU stay (level 2 care) / hospital stay, mean (SD) by treatment group
- Health service contacts up to 12 months post randomisation, mean (SD) by treatment

7.7 Health Economics

- Incremental cost effectiveness ratio (ICER)
- Presentation of the incremental net benefit (INB) and its sampling uncertainty, diagrammatically as a function of the willingness-to-pay threshold.
- Presentation of the joint uncertainty in costs and effects on the cost-effectiveness plane
- Cost-effectiveness acceptability curve (CEAC)
- The results of the sensitivity analysis will be presented in a table showing the impact of variations in key parameters on the results of the cost-effectiveness analysis.

8. ADDITIONAL INFORMATION

8.1 Trial Steering Committee

The conduct of the trial will be overseen by a Trial Steering Committee (TSC), a group of experienced critical care personnel and trialists as well as a 'lay' representative and a senior member of staff from the CTU. Biannual meetings will be held and will be formally minuted. The TSC, in the development of this protocol and throughout the trial will take responsibility for monitoring and guiding overall progress, scientific standards, operational delivery and protecting the rights and safety of trial participants.

8.2 Data Monitoring and Ethics Committee

A DMEC has been appointed comprising two clinicians with experience in undertaking clinical trials / caring for critically ill patients and a statistician who are independent of the trial. Biannual meetings are being held and formally minuted. The DMEC's responsibility is to safeguard the interests of the trial participants, in particular with regard to safety and assist and advise the TSC so as to protect the validity and credibility of the trial. The DMEC monitors recruitment, adverse events and outcome data.

During the recruitment period, reports are provided to the DMEC which include information on the AEs reported, deaths from all causes at 28 days and recruitment, along with any other data that the committee may request.

The DMEC will advise the TSC if, in their view, the randomised comparisons have provided both (i) 'proof beyond reasonable doubt' that for all, or some, the treatment is clearly indicated or clearly contra-indicated and (ii) evidence that might reasonably be expected to materially influence future patient management. Following a report from the DMEC, the TSC will decide what actions, if any, are required. Unless the DMEC request cessation of the trial the TSC and the collaborators will not be informed of the interim results.

9. SIGNATURES OF APPROVAL

Date: 21st October 2013
Version: 3.0

This document has completed a final review and is understood and approved by the following:

Professor Danny McAuley Chief investigator	*Chief Investigator signature*	22.10.2013 Date dd/mm/yyyy
Professor John Laffey Chief investigator	*Chief Investigator signature*	20/12/2013 Date dd/mm/yyyy
Evie Gardner Senior Statistician	*Senior Statistician signature*	21/10/2013 Date dd/mm/yyyy
Cliona McDowell Trial Statistician	*Trial Statistician Signature*	21/10/2013 Date dd/mm/yyyy

APPENDIX 1: EXAMPLE DRAFT SUMMARY TABLES

Table xx. Baseline Characteristics at trial entry

	Simvastatin n = (%)	**Placebo n = (%)**
Age (years)		
Gender Male Female		
Sepsis Non Sepsis		
Vasopressor Requirement		
Plateau Pressure (cmH_2O)		
APACHE II score		
PaO_2:FiO_2 ratio:		
Tidal Volume (ml/kg Ideal Body Weight)		
Aetiology of ARDS Direct Smoke/toxin inhalation Gastric content aspiration Near drowning Thoracic trauma Pneumonia Other Indirect Sepsis Cardiopulmonary bypass Pancreatitis Non-thoracic trauma Other		
SOFA Score		
Oxygenation Index		
Lowest Mean Arterial Pressure (mmHg)		

Mean (SD) presented for continuous variables and no. (%) for all categorical variables.

Table xx. Treatment after Trial Entry

	Simvastatin n = (%)	**Placebo n = (%)**
Study drug given No. of days on treatment*		
Reasons for termination of study drug 28 days after randomisation Discharge from Critical Care Liver Transaminases>8 times upper limit normal Creatinine Kinase>10 times upper limit normal Request from PerLR/ProfLR/patient Discontinuation of active treatment Development of a condition requiring immediate treatment with statin Decision by a Physician on safety grounds Death Other		
Non trial statins Days of non trial statins		
Protocol violations: Post-randomisation withdrawal Refused use of data already collected Refused data collection from NHS records Withdrew from follow-up Ineligible patient Did not receive allocated treatment Received treatment of other group		

*Mean (SD) no. of days on treatment

Table xx: Main Clinical Outcome variables

	Simvastatin n = (%)	Placebo n = (%)	Difference (95% CI)	p-value
Primary outcome; VFDs to 28 days post randomisation*				
Non pulmonary OFFDs in first 28 days				
Change in Oxygenation Index from baseline Day 3 Day 7 Day 14 Day 28				
Change in SOFA Day 3 Day 7 Day 14 Day 28				
All cause mortality 28 days post randomisation[#]				
Death before discharge from critical care[#]				
Death before discharge from hospital [#]				

Mean (SD) presented for treatment arms
*Results from bootstrapped t-test also presented
[#]No. (%) for treatment arms and Risk Ratio and 95% CI presented

Table xx: Safety by Treatment Group

		Simvastatin n = (%)	Placebo n = (%)
AEs, SAEs and SUSARs	Total SAES		
	Related to study drug		
	Related to study drug and unexpected		
	Total AES		
	Related to study drug		
SAEs	Cardiac Arrhythmia		
	Cardiac General		
	Gastrointestinal		
	Etc…..		
AEs	Cardiac Arrhythmia		
	Cardiac General		
	Gastrointestinal		
	Etc…..		
Adverse Reactions	CK>10 times the upper limit of normal		
	ALT>8 times the upper limit of normal		
	AST>8 times the upper limit of normal		
Serious Adverse Reactions	Need for renal replacement therapy in patients with CK elevated>10 fold		

Health economics tables (Will form part of Secondary report on long term outcomes)

Table xx: Resource use over 12 months according to allocation group

Resource use variable	Simvastatin (n=) Mean (SD)	Placebo (n=) Mean (SD)	p-value
Primary hospital admission			
ICU stay (days)			
HDU stay (days)			
Ward stay (days)			
GP			
at the GP practice (visits)			
Telephone (calls)			
Home (visits)			
Nurse			
at GP practice (visits)			
Telephone (calls)			
Home (visits)			
Rapid response team / Acute Care at Home team (visits)			
Social worker (visits)			
Physiotherapist (visits)			
Occupational Therapist (visits)			
Other hospital stay (days)			
Hospital outpatient clinic (visits)			
Hospital accident and emergency (visits)			
Home help (visits)			
Meals on wheels (visits)			
Carer (visits)			
Other (please specify) e.g. day centre			

Table xx: Mean (95% CI) cost (£) of resource use over 12 months according to allocation group

Resource use variable	Simvastatin (n=) Mean (95% CI)	Placebo (n=) Mean (95% CI)
Primary hospital admission		
ICU stay (days)		
HDU stay (days)		
Ward stay (days)		
GP		
at the GP practice (visits)		
Telephone (calls)		
Home (visits)		
Nurse		

at GP practice (visits)		
Telephone (calls)		
Home (visits)		
Rapid response team / Acute Care at Home team (visits)		
Social worker (visits)		
Physiotherapist (visits)		
Occupational Therapist (visits)		
Other hospital stay (days)		
Hospital outpatient clinic (visits)		
Hospital accident and emergency (visits)		
Home help (visits)		
Meals on wheels (visits)		
Carer (visits)		
Other (please specify) e.g. day centre		
Total costs		
Difference (95% CI) in mean costs		

Table xx: Utilities and QALYs over 12 months according to allocation treatment group

	Simvastatin (n=)	Placebo (n=)
Mean (SD) utility from EQ-5D		
Baseline		
Discharge		
3 months		
6 months		
12 months		
Mean (SD) QALYs over 12 months		
Difference (95% CI) in mean QALYs		