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

(HARP-2)

Acronym:	HARP-2
Protocol Number:	10072DMcA-CS
Version Number / Date:	2.0 / 01-Sep-2010
EudraCT Number:	2010-020763-20
ISRCTN:	Application pending
EME Reference Number:	08/99/09
Amendments to Date:	None
Chief Investigator for UK:	Professor Danny McAuley Professor / Consultant Centre for Infection and Immunity Queen's University, Belfast Microbiology Building Grosvenor Road Belfast, BT12 6BN Northern Ireland
Chief Investigator for Ireland:	Professor John Laffey Professor and Head of Department Department of Anaesthesia and Intensive Care Clinical Science Institute National University of Ireland Galway Costello Road Newcastle Galway, Ireland

PROTOCOL AUTHORISATION

Full Protocol Title: Hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in Acute lung injury to Reduce Pulmonary dysfunction (HARP-2)

Protocol Number: 10072DMcA-CS

Version Number / Date: 1.0 / 24-Jun-2010
2.0 / 01-Sep-2010

A review of the protocol has been completed and is understood and approved by the following:

_____	_____	_____/_____/_____
Chief Investigator	Chief Investigator Signature	Date dd/mm/yyyy
_____	_____	_____/_____/_____
Statistician	Statistician Signature	Date dd/mm/yyyy

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Full Wording
ACR	Albumin Creatine Ratio
AE	Adverse Event
ALI	Acute Lung Injury
ALT	Alanine Transaminase
AR	Adverse Reaction
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Aminotransferase
BHSCT	Belfast Health and Social Care Trust
BNF	British National Formulary
CEA	Cost Effectiveness Analysis
CEAC	Cost Effectiveness Acceptability Curve
CI	Chief Investigator
CI	Confidence Intervals
CK	Creatine Kinase
CONSORT	Consolidated Standards of Reporting Trials
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
CritPal	Critical Care Patient Liaison Committee
CRP	C-Reactive Protein
CRSC	Clinical Research Support Centre
CTA	Clinical Trial Authorisation
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
DNA	Deoxyribonucliec Acid
ECM	Extracellular Matrix
EME	Efficacy and Mechanism Evaluation
EudraCT	European Union Drug Regulating Authorities Clinical Trials
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
ICCTG	Irish Critical Care Trials Group
ICH	International Conference of Harmonisation
ICER	Incremental Cost Effectiveness Ratio
ICU	Intensive Care Unit
IL	Interleukin
IMB	Irish Medicines Board
IMP	Investigational Medicinal Product
INB	Incremental Net Benefit
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
LPS	Lipopolysaccharide
MHRA	Medicine and Healthcare Products Regulatory Agency
MMPs	Matrix Metalloproteinases
MPO	Myeloperoxidase
MRC	Medical Research Council
MREC	Multi-Centre Research Ethics Committee
NE	Neutrophil Elastase
NETSCC	NIHR Evaluation Trials and Studies Coordinating Centre
NF-kB	Nuclear factor kappa B
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIH	National Institutes of Health
NIHR	National Institute of Health Research
NUI	National University of Ireland

OI	Oxygenation Index
PAOP	Pulmonary Arterial Occlusion Pressure
PerLR	Personal Legal Representative
PI	Principal Investigator
PIS	Participant Information Sheet
ProfLR	Professional Legal Representative
PSSRU	Personal Social Services Research Unit
QALY	Quality Adjusted Life Year
QUB	Queen's University Belfast
REC	Research Ethics Committee
ROI	Republic of Ireland
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Standard Deviation
SOFA	Sequential Organ Failure Assessment
SOPs	Standard Operating Procedures
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TNFα	Tumour Necrosis Factor Alpha
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
UKCRN	United Kingdom Clinical Research Network
VFD	Ventilator Free Days

1 TRIAL SUMMARY

1.1 Trial Phase: Phase II

1.2 Trial Aims and Objectives: The aim 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.

1.3 Patient Population: Patients with ALI

1.4 Trial Setting: Adult intensive care units (ICU)

1.5 Trial Intervention: Simvastatin 80mg once daily administered enterally via a feeding tube or orally for up to 28 days

1.6 Concurrent Control: Identical placebo once daily administered enterally via a feeding tube or orally for up to 28 days

1.7 Sample Size: 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 ventilator-free days (VFDs). With an estimated dropout rate of 3%, this study will require a total of 540 patients (270 in each group)

1.8 Method of Participant Assignment: Patients will be individually randomised after informed consent has been obtained and eligibility confirmed

1.9 Examination Points: Daily up to day 28, at discharge, 3, 6 and 12 months

1.10 Primary Outcome: The primary outcome will be VFDs

1.11 Secondary Outcomes: There are a number of secondary outcomes which include: (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) All cause mortality 28 days post randomisation; (d) Mortality at (first) discharge from ICU; (e) Mortality at (first) discharge from hospital; (f) Mortality at 12 months post randomisation; (g) Safety; (h) Biological mechanisms; (i) Health-related quality of life; (j) Cost effectiveness.

2 TRIAL TEAM

Chief Investigator for UK:	Professor Danny McAuley, Professor/Consultant, Centre for Infection and Immunity, Queen's University Belfast, Microbiology Building, Grosvenor Road, Belfast, BT12 6BN, Northern Ireland, UK
Chief Investigator for Ireland:	Professor John Laffey, Professor and Head of Department, Department of Anaesthesia and Intensive Care, Clinical Science Institute, National University of Ireland Galway, Costello Road, Newcastle, Galway, Ireland
Co-Investigators:	Dr Cecilia O'Kane, Senior Lecturer and Consultant, Queen's University Belfast, Microbiology Building, Grosvenor Road, Belfast BT12 6BN, Northern Ireland, UK
	Professor Cliff Taggart, Chair in Oral Science, Centre for Infection and Immunity, Queen's University Belfast, Whitla Medical Building, 97 Lisburn Road, Belfast, BT9 7BL, Northern Ireland, UK
Clinical Trials Unit: (Trials Co-ordinating Centre)	Dr Grainne Crealey, Acting Director, Clinical Research Support Centre, Education & Research Centre, The Royal Hospitals, Grosvenor Road, Belfast, BT12 6BA, Northern Ireland, UK
Statistician:	Mr Mike Stevenson, Statistician, Clinical Research Support Centre, Education & Research Centre, The Royal Hospitals, Grosvenor Road, Belfast, BT12 6BN, Northern Ireland, UK
Health Economist:	Dr Grainne Crealey, Senior Health Economist, Clinical Research Support Centre, Education & Research Centre, The Royal Hospitals, Grosvenor Road, Belfast, BT12 6BN, Northern Ireland, UK
UK Trial Sponsor	Professor Ian Young, Associate Medical Director, Belfast Health and Social Care Trust (BHSCT), The Royal Hospitals, Grosvenor Road, Belfast, BT12 6BN, Northern Ireland, UK
Ireland Trial Sponsor	Professor Terry Smith, Vice President for Research, National University of Ireland (NUI) Galway University Road Galway, Ireland

3 BACKGROUND

3.1 Background Information

Acute lung injury (ALI) is a common devastating clinical syndrome characterised by life-threatening respiratory failure requiring mechanical ventilation and multiple organ failure and are a major cause of morbidity and mortality. The acute respiratory distress syndrome (ARDS) is a more severe form of ALI defined on the basis of impaired oxygenation. ALI occurs in response to a variety of insults, such as trauma and severe sepsis. It affects all age groups; has a high mortality of up to 30-50% [1, 2] and causes a long-term reduction in quality of life for survivors [3]. ALI has significant resource implications, prolonging intensive care unit (ICU) and hospital stay, and requiring rehabilitation in the community [4]. The cost per ICU bed-day exceeds £1800 and delivery of critical care to patients with ALI accounts for a significant proportion of ICU capacity. Based on available data, in the UK and Ireland it is estimated that up to 45000 cases of ALI occur, with an estimated 13000-22000 deaths per year in patients with ALI [1, 2, 5]. Only 54% of survivors are able to return to work 12 months after hospital discharge [6]. The high incidence, mortality, long-term consequences and high economic costs mean that ALI is an extremely important problem.

3.2 Rationale for the Trial

3.2.1 Statins can modulate mechanisms important in the pathogenesis of ALI

The pathogenesis of ALI involves pulmonary recruitment of macrophages and neutrophils. These cells are in an activated state characterised by upregulated expression of cell surface adhesion molecules, excessive cytokine production (tumour necrosis factor alpha (TNFα), interleukin (IL)-1β, IL-6, IL-8 and IL-10) and extracellular release of biologically active cytotoxic proteases including neutrophil elastase (NE) and matrix metalloproteinases (MMPs) [7]. The resulting injury to alveolar epithelium and endothelium, which can be detected biochemically, determines the severity of lung injury [8].

There is a large body of evidence from in vitro and animal studies that statins may be beneficial in ALI which we have recently reviewed [9]. In summary, statins improve epithelial and endothelial function to reduce alveolar capillary permeability and reduce pulmonary oedema. In addition they modulate the inflammatory cascade; regulate inflammatory cell recruitment, activation and apoptosis; and reduce cytokine and protease activity. This may improve outcomes, as high levels and persistence of inflammatory mediators in ALI are associated with poor outcome [10].

3.2.2 Observational studies support a clinical trial of a statin in ALI

ALI is the most common complication of severe sepsis [11]. In patients with sepsis most [12-15] observational studies suggest that statins are associated with better outcomes, as measured by morbidity and mortality. Similarly, most [16-18] observational studies have suggested a beneficial effect of statins in

patients with pneumonia, supporting a potential role for statins in modulating pulmonary inflammation.

The Irish Critical Care Trials Group (ICCTG) have undertaken a prospective observational study in patients with ALI, which found mortality was lower in patients receiving statins during their ICU stay. After adjusting for plateau pressure, severity of illness and other relevant covariates in a multiple logistic regression model, patients receiving statins had a much lower probability of death, although this failed to reach significance (OR 0.27, 95% CI 0.06-1.21 p=0.09) [5]. Similarly, in a recent retrospective study, statin usage in patients with ALI was associated with increased VFDs and reduced mortality, although again this was not significant [19]. These observational studies were not powered to examine the effect of statins on mortality.

It is not clear if the association with better outcomes in these studies is due to statins as opposed to statins representing a surrogate marker for improved access to healthcare. Moreover, these studies do not demonstrate whether beneficial effects will occur when statins are commenced after the onset of ALI. Although it is encouraging that statins are a potentially beneficial pharmacological treatment in ALI, a trial powered for important clinical outcomes is required.

3.2.3 Simvastatin reduces lipopolysaccharide-induced pulmonary and systemic inflammation in humans

We have conducted a study to examine if simvastatin modulates pathogenic mechanisms important in the development of lung injury in a model of acute lung inflammation induced by inhaled lipopolysaccharide (LPS) in healthy human volunteers [20]. In this double-blind, placebo-controlled study, participants were randomised to simvastatin or placebo orally for 4 days prior to LPS inhalation. Pre-treatment with simvastatin reduced mediators of early ALI in bronchoalveolar lavage fluid, including TNFα; neutrophil myeloperoxidase (MPO); and protease release as measured by NE and MMP-7, -8 and -9. Furthermore, there was a significant reduction in systemic inflammation as measured by plasma C-reactive protein (CRP). These effects were associated with reduced nuclear factor kappa B (NF-κB) translocation. These novel findings provide the first proof of principle that simvastatin has important anti-inflammatory effects in vivo in humans challenged with aerosolised endotoxin. These mechanistic findings are supported by a randomised placebo-controlled study that found simvastatin 80mg for 4 days reduced systemic cytokine responses induced by low dose intravenous LPS in healthy subjects [21]. Finally a randomised placebo-controlled study in patients with acute bacterial infection found that simvastatin, commenced prior to the development of sepsis-induced organ dysfunction, also reduced the levels of systemic inflammatory cytokines (TNFα and IL-6) [22].

3.2.4 Proof of concept that simvastatin improves pulmonary and non-pulmonary organ dysfunction, reduces inflammation and is well tolerated in patients with ALI.

We have completed a single centre, randomised, double-blind, placebo-controlled phase II study of simvastatin (80mg for up to 14 days) in 60 patients with ALI. By day 14, there was a trend to improvements in pulmonary dysfunction, as measured by oxygenation index (OI), respiratory system compliance and lung injury score in the simvastatin-treated group non-pulmonary organ dysfunction, as measured by Sequential Organ Failure Assessment (SOFA) score was significantly lower in the simvastatin-treated group, with improvements in cardiovascular, renal and coagulation function. There was no difference in outcome for patients with sepsis or non-sepsis related ALI. Importantly simvastatin 80mg was well tolerated with no increase in adverse events (AEs). In addition, we found that unlike placebo, simvastatin decreased pulmonary IL-8 by 2.5 fold by day 3 with a trend to a decrease in IL-6 by 2.9 fold. In addition, at day 14 plasma CRP was lower with a trend to reduced plasma IL-6 in the simvastatin-treated group.

Together these results reflect the beneficial effects seen in previous in vitro and animal studies. These measures are independent and so each provides corroborating evidence of a beneficial effect of simvastatin in patients with ALI. The study described above was not designed or powered to show an effect of simvastatin on VFDs or mortality. However pulmonary and non-pulmonary organ dysfunction as well as high levels of inflammatory cytokines are associated with fewer VFDs and higher ICU mortality which suggests that simvastatin may lead to improved clinical outcomes.

The findings above are supported by two small prospective randomised controlled studies involving the acute use of statins in patients with sepsis and pneumonia. These studies have not yet been published except in abstract form. Choi et al. studied atorvastatin 10mg once daily in 74 patients with sepsis and pneumonia [23]. Hospital mortality was reduced in the atorvastatin group compared to placebo although this failed to reach significance (47 versus 53%; p=0.06). Similarly Gonzalez et al. conducted a study of simvastatin 80mg once daily or placebo for 14 days in 40 patients with sepsis and found simvastatin decreased hospital length of stay [24].

3.2.5 The intervention has acceptable side effects

Statins have been proven to be a well-tolerated class of drugs. An improved mortality rate and no AEs have been reported in observational studies in critically ill patients with sepsis who were receiving statins [12-18]. Importantly no toxicity was reported when statins were continued throughout the ICU course.

Simvastatin 80mg is within the licensed therapeutic range for the treatment of hypercholesterolaemia. Although a different patient population, there is evidence regarding the safety of simvastatin 80mg in patients with cardiovascular disease. In a study where 2265 patients following an acute coronary syndrome were randomised to receive simvastain 80mg, myopathy

(Creatine Kinase (CK) >10 times the upper limit of normal associated with muscle symptoms) occurred in only 0.4% and rhabdomyolysis (CK > 10000 units/L with or without muscle symptoms) in 0.13% receiving simvastatin 80mg [25]. Importantly in this study, follow-up was only at months 1, 4, and 8 and every 4 months thereafter for up to 24 months until trial completion. In a further study where 6031 patients with a history of a previous myocardial infarction were randomised to receive simvastain 80mg, myopathy occurred in 0.9% and rhabdomyolysis in 0.18% receiving simvastatin 80mg [26]. In this study participants were seen for follow-up only at 2, 4, 8, and 12 months, and then at 6-month intervals with a median follow-up of 6 years. It is important to emphasis the maximum treatment period with simvastatin 80mg in this study is 28 days with safety monitoring (CK and liver transaminases) at days 3, 7, 14 and 28.

The data from our proof of concept study reassuringly found simvastatin 80mg was well tolerated and not associated with increased adverse events (AEs) compared to placebo. There was no difference in CK levels or numbers of patients with a CK >10 times the upper limit of normal between the groups. There were no differences in creatinine levels between the groups. Reassuringly there was a trend towards a lower incidence of renal replacement therapy at day 14 in the simvastatin-treated group. Liver transaminases (alanine transaminase (ALT) and aspartate aminotransferase (AST)) were commonly elevated and although not significant this was more common in the placebo-treated group. There were no differences in AEs or serious adverse events (SAEs) between the groups. No drug-related SAEs occurred during the study (Table 1).

Table 1: Safety data

	Simvastatin	Placebo	p value
CK > 10 times ULN* (%)	4.5	8.7	0.58
ALT > 3 times ULN* (%)	4.4	8.0	0.60
AST > 3 times ULN* (%)	8.3	16.7	0.34
Adverse events (%)	47	43	0.79
Serious adverse events (%)	20	23	0.75

* upper limit of normal

While there are data showing that high plasma concentrations of statins are achieved in patients in ICU compared to normal controls [27, 28], in our proof of concept study (unpublished data) this was not associated with increased toxicity. In 3 recent randomised studies in patients with sepsis there was no increased incidence of drug-related AEs [23, 24, 29]. Additionally this confirms reliable drug delivery is achieved with the enteral route of administration.

The risks to participants will be minimised by several elements of the study design. The exclusion criteria prevent participation of patients who might be at increased risk of statin-related adverse effects. In addition, patients who have co-existing conditions that would benefit from statins as part of standard clinical care will be excluded. There will be an emergency unblinding protocol in the event of any life-threatening situation where knowledge of a patient's

allocation is necessary. Finally, we will closely monitor for liver and muscle dysfunction. Treatment will be discontinued if CK levels are elevated >10 times the upper limit or if serum transaminases are elevated >5 times the upper limit of the normal range.

3.2.6 Rationale for choice of simvastatin

The diverse effects of statins appear to represent a class effect. As outlined above, in both in vitro and animal experiments statins show consistent effects regardless of the choice of statin. In addition retrospective and prospective human studies have included multiple statins and shown beneficial effects. However, as the only statin with proof of concept efficacy and safety data in ALI, simvastatin will be investigated in this study.

3.2.7 Rationale for simvastatin 28-day duration of treatment

The decision to examine treatment for up to 28 days is based on: 1) data from our proof of concept study demonstrating ongoing clinical improvement to day 14; 2) data that the upper interquartile range for duration of ICU stay in patients with ALI/ARDS is 14-18 days [1, 5]; and 3) observational trials showing benefit with no reported toxicity when statins were continued throughout the ICU stay.

3.2.8 Rationale for simvastatin 80mg dosage

Although there is a large amount of data suggesting statins may be beneficial in animal models of ALI, only a single animal study has compared 2 doses of simvastatin (5 or 20 mg/kg given intraperitoneally 24 hours before and concomitantly with LPS to induce lung injury) and only the higher dose was effective in attenuating lung injury [30].

Importantly, a recent retrospective observational study of statin usage in patients with sepsis found a greater mortality benefit in patients who were receiving a higher dose of statin [31].

Simvastatin 80mg is the only dose with proof of concept data and is well tolerated in ALI and therefore simvastatin 80mg versus placebo once daily will be investigated in this study.

Although it is acknowledged that the risk of adverse side effects is dose related, on the basis of available evidence, simvastatin 80mg is safe, particularly given the duration of treatment is only up to 28 days and these patients will be intensively monitored.

3.2.9 There are no effective pharmacological therapies for ALI

The Cochrane systematic review of pharmacological treatments that included 22 studies of 14 different drugs concluded that “effective pharmacotherapy for ALI is extremely limited, with insufficient evidence to support any specific intervention” [32].

The National Heart, Lung and Blood Institute Working Group considered the future research directions in ALI in 2002 and concluded that clinical trials underpinned by mechanistic investigations were essential to develop new therapies for ALI [33].

3.2.10 Lack of published randomised controlled trials of statins in ALI

We have conducted a systematic review, searched registries of ongoing clinical trials and contacted national and international experts in ALI. The National Institutes of Health (NIH) has recently commenced a phase III multi-centre trial of rosuvastatin versus placebo for up to 28 days in patients with sepsis-induced respiratory failure in the United States. Our trial will examine simvastatin and investigate ALI due to all aetiologies, as well as study the potential mechanism of action by which statins act. In addition, unlike the US trial, an economic evaluation will be undertaken. We have confirmed there have been and are no other trials of statins in ALI currently underway.

3.2.11 The proposed trial is supported by the critical care community

At a critical care research strategy meeting held by the ICCTG and the Intensive Care Society of Ireland to assess the feasibility of undertaking ICU-based multi-centre randomised clinical trials (06/2008), this trial was most highly ranked by active ICU clinicians.
The study has been discussed with national and international experts with experience in undertaking clinical trials in the critically ill and in patients with ALI (including Dr D Young; Chief Investigator on an National Institute of Health Research Evaluation Trials and Studies Coordinating Centre (NETSCC) Health Technology Assessment (HTA) programme funded study of high frequency ventilation in ARDS (OSCAR) and Prof T Walsh; Chair of the UK Clinical Research Network Critical Care Specialty Group as well as Prof J Truwitt and Prof G Bernard from the NIH-funded ARDS clinical trials network). The study was also presented at the UK Critical Care Trials Forum (06/2009). Feedback has consistently indicated that there is a need for this trial; that the planned intervention (dose and duration of treatment) is well considered; that the primary endpoint is appropriate; and that the trial is well designed to address the research question.

3.2.12 The intervention is simple and inexpensive

Simvastatin is an inexpensive treatment readily available from generic drug manufacturers and costs less than £5 for 28 days' treatment. By comparison the cost per ICU bed-day exceeds £1800.

4 TRIAL AIMS and OBJECTIVES

4.1 Trial Aim

The aim of this study 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 ALI.

4.2 Trial Objectives

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.

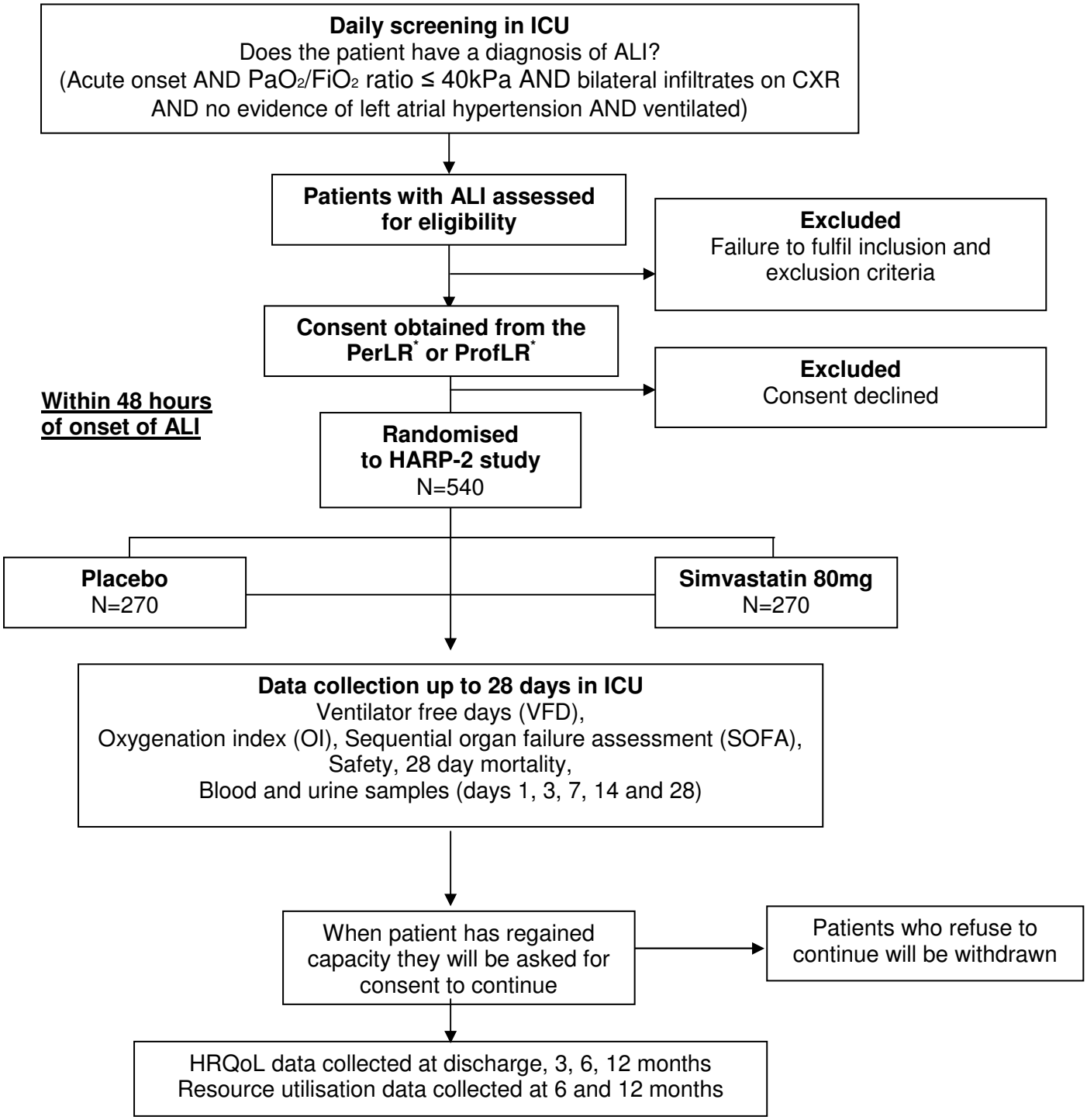
Objective 2: To study the biological mechanisms of simvastatin treatment on: (2a) systemic markers of inflammation; (2b) systemic cell-specific indices of activation and injury to the alveolar epithelium and endothelium; (2c) lung extracellular matrix degradation; (2d) assess whether response to simvastatin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

5 TRIAL DESIGN

5.1 Design of Trial

Prospective, randomised, double-blind, placebo-controlled phase II multi-centre trial of simvastatin in patients with ALI.

5.2 Trial Schematic Diagram



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

5.3 Trial Sites

Adult general ICUs will be selected on the basis of the following criteria.

1. Willingness to participate in the trial
2. Evidence that they have access to the patient population
3. Evidence of suitable facilities and resources to participate
4. Documented willingness to comply with the protocol, SOPs, the principles of GCP and regulatory requirements

5.4 Trial Patients

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

5.4.1 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

5.4.2 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 >5 times the upper limit of the normal range

6. Patients currently receiving ongoing and sustained treatment with any of the following; itraconazole, ketoconazole, erythromycin, clarithromycin, 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
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

5.5 Duration of Trial

540 patients will be recruited over approximately 31 months, from at least 14 adult general ICUs. Following randomisation patients will participate in this clinical trial for up to 12 months.

5.6 Trial Interventions

Patients will be randomised to receive once daily simvastatin 80mg (as two 40mg tablets) or 2 identical placebo tablets administered enterally via a feeding tube or orally for up to 28 days.

Simvastatin administered enterally via a feeding tube is well absorbed in the critically ill. Importantly, absorption is not impaired in the setting of delayed gastrointestinal motility as determined by high nasogastric aspirates (unpublished data).

5.7 Outcome Measures

5.7.1 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.

In keeping with previous trials [35, 36], unassisted breathing is defined as:

a) extubated with supplemental oxygen or room air; or
b) open T-tube breathing; or
c) tracheostomy mask breathing; or
d) Continuous Positive Airway Pressure (CPAP) ≤5 cm H20 without pressure support

Patients receiving pressure support via non-invasive ventilation will be defined as receiving assisted ventilation.

5.7.2 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.

5.7.2.1 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. All cause mortality 28 days post randomisation
4. Mortality at (first) discharge from ICU
5. Mortality at (first) discharge from hospital
6. Mortality at 12 months post randomisation

5.7.2.2 Safety

1. CK >10 times the upper limit of normal (measured on days 1, 3, 7, 14 and 28)
2. ALT/AST >5 times the upper limit of normal (measured on days 1, 3, 7, 14 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

5.7.2.3 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

5.7.2.4 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 hospital stay
   Health service contacts up to 12 months post randomisation

6. TRIAL PROCEDURES

6.1 Screening Procedure

Patients will be prospectively screened daily, on the basis of the inclusion/exclusion criteria as specified in the protocol by the local ICU clinicians. Each Principal Investigator (PI) must retain a screening log and only those patients with ALI must be entered into the screening log which will be completed by the investigator or designee. If the patient is not recruited the reason for not being enrolled on the trial must also be recorded on the screening log.

6.2 Informed Consent Procedure

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. Eligible patients may only be included in the trial after obtaining written informed consent. Informed consent must be obtained prior to conducting any trial specific procedures and the process for obtaining informed consent must be documented in the patient's medical records (source documents which will be reviewed at the

time of on site monitoring visits). Informed consent will also be obtained specifically for genetic testing. Similar consent mechanisms have been used successfully in other trials in similar populations [37].

6.2.1 Informed Consent Procedure for UK

Informed consent forms approved by the Research Ethics Committee (REC) will be provided to each trial site. The PI is responsible for ensuring that informed consent for trial participation is given by each patient or a legal representative. This requires that the informed consent form be signed and personally dated by the patient or by the patient's legally acceptable representative. An appropriately trained doctor or nurse may take consent. If no consent is given a patient cannot be randomised into the trial.

The incapacitating nature of the condition precludes obtaining prospective informed consent from participants. In this situation informed consent will be sought from a Personal Legal Representative (PerLR) or Professional Legal Representative (ProfLR) should no PerLR be available.

6.2.1.1 Personal Legal Representative Consent

Informed consent will be sought from the patient's PerLR who may be a relative, partner or close friend. The PerLR will be informed about the trial by the responsible clinician or a member of the research team and they will be provided with a copy of the Covering Statement for the PerLR with an attached Participant Information Sheet (PIS) and asked to give an opinion as to whether the patient would object to taking part in such medical research. If the PerLR decides that the patient would have no objection to participating in the trial they will be asked to sign two copies of the PerLR Consent Form, which will then be countersigned by the person taking consent. A copy of the signed informed consent form will be placed in the patients' medical records, whilst the originals will be retained by the PerLR and by the PI in the Investigator Site File (ISF).

6.2.1.2 Professional Legal Representative Consent

If the patient is unable to give informed consent and no PerLR is available, a doctor who is not connected with the conduct of the trial may act as a ProfLR. The doctor will be informed about the trial by the responsible clinician or a member of the research team and given a copy of the PIS. If the doctor decides that the patient is suitable for entry into the trial they will be asked to sign two copies of the ProfLR Consent Form. A copy of the signed informed consent form will be placed in the patients' medical records, whilst the originals will be retained by the doctor ProfLR and by the PI in the ISF.

6.2.1.3 Retrospective Patient Consent

Patients will be informed of their participation in the trial by the responsible clinician or a member of the research team once they regain capacity to understand the details of the trial. The responsible clinician or a member of the research team will discuss the study with the patient and the patient will be

given a copy of the PIS to keep. The patient will be asked for consent to participate in the trial and to sign two copies of the Consent to Continue Form, which will then be countersigned by the person taking consent. A copy of the signed Consent Form will be placed in the patient' medical records whilst the originals will be retained by the patient and by the PI in the ISF. Where consent to continue is not obtained, consent from the legal representative will remain valid. If the patient refuses consent, data collected about the patient will not be entered into the analysis.

6.2.1.4 Withdrawal of Consent

Patients may withdraw or be withdrawn (by PerLR or ProfLR) from the trial at any time without prejudice. Data recorded up to the point of withdrawal will be included in the trial analysis, unless consent to use their data has also been withdrawn. If a patient or legal representative requests termination of the trial drug during the treatment period, the drug will be stopped but the patient will continue to be followed-up as part of the trial. If a patient or a PerLR withdraws consent during trial treatment, the trial drug will be stopped but permission will be sought to access medical records for data related to the trial. If a patient or PerLR wishes to withdraw from the trial after completion of trial treatment, permission to access medical records for trial data will be sought.

6.2.2 Informed Consent Procedure for Ireland

Informed consent forms approved by the Research Ethics Committee (REC) will be provided to each trial site. The PI is responsible for ensuring that informed consent/assent for trial participation is given by each patient or their representative, respectively. This requires that the informed consent/assent form be signed and personally dated by the patient or by their representative, respectively. An appropriately trained doctor or nurse may take consent. If no consent is given a patient cannot be randomised into the trial.

The incapacitating nature of the condition precludes obtaining prospective informed consent from participants. In this situation informed assent will be sought from the Patient's Representative or from a Professional Representative should no suitable representative be available.

6.2.2.1 Patient Representative Assent

Informed assent will be sought from the patient's Representative who may be a relative, partner or close friend. The Patient Representative will be informed about the trial by the responsible clinician or a member of the research team and they will be provided with a copy of the Covering Statement for the representative with an attached Participant Information Sheet (PIS) and asked to give an opinion as to whether the patient would object to taking part in such medical research. If the patient representative decides that the patient would have no objection to participating in the trial they will be asked to sign two copies of the Patient Representative Assent Form, which will then be countersigned by the person taking consent. A copy of the signed informed

assent form will be placed in the patients' medical records, whilst the originals will be retained by the Patient Representative and by the PI in the ISF.

6.2.2.2 Professional Representative Assent

If the patient is unable to give informed consent and no Patient Representative is available, a doctor who is not connected with the conduct of the trial may act as a Professional Representative. The doctor will be informed about the trial by the responsible clinician or a member of the research team and given a copy of the PIS. If the doctor decides that the patient is suitable for entry into the trial they will be asked to sign two copies of the Professional Representative Assent Form. A copy of the signed informed assent form will be placed in the patients' medical records, whilst the originals will be retained by the Professional Representative and by the PI in the ISF.

6.2.2.3 Retrospective Patient Consent

Patients will be informed of their participation in the trial by the responsible clinician or a member of the research team once they regain capacity to understand the details of the trial. The responsible clinician or a member of the research team will discuss the study with the patient and the patient will be given a copy of the PIS to keep. The patient will be asked for consent to participate in the trial and to sign two copies of the Consent to Continue Form, which will then be countersigned by the person taking consent. A copy of the signed Consent Form will be placed in the patient' medical records whilst the originals will be retained by the patient and by the PI in the ISF. Where consent to continue is not obtained, consent from the Patient or Professional Representative will remain valid. If the patient refuses consent, data collected about the patient will not be entered into the analysis.

6.2.2.4 Withdrawal of Consent/Assent

Patients may withdraw or be withdrawn (by the Patient or Professional Representative) from the trial at any time without prejudice. Data recorded up to the point of withdrawal will be included in the trial analysis, unless consent to use their data has also been withdrawn. If a Patient or Professional Representative requests termination of the trial drug during the treatment period, the drug will be stopped but the patient will continue to be followed-up as part of the trial. If a patient or a Patient Representative withdraws consent/assent during trial treatment, the trial drug will be stopped but permission will be sought to access medical records for data related to the trial. If a patient or Patient Representative wishes to withdraw from the trial after completion of trial treatment, permission to access medical records for trial data will be sought.

6.3 Patient Registration and Randomisation Procedure

After informed consent, patients will be randomised using an automated 24-hour telephone randomisation service. Randomisation will be stratified by site and by vasopressor requirement (defined as any inotropic requirement except dopamine < 6mcg/kg/min). Each site participating in the study will have a

unique site number which must be entered when using the randomisation system. The randomisation service will ask to be provided with confirmation that the patient fulfils the trial entry criteria and the data required for stratification. The randomisation service will allocate a unique trial identifier to each patient in accordance with the study randomisation schedule prepared prior to the start of the trial. The unique trial identifier allocated at the time of randomisation will be used throughout the trial for purposes of patient identification. The randomisation service will confirm randomisation details by email to the Clinical Trials Unit (CTU) and to the study site.

.

6.4 Trial Treatments

Patients will be randomised to receive once daily simvastatin 80mg (as two 40mg tablets) or 2 identical placebo tablets administered entrally via a feeding tube or orally for up to 28 days. Treatment allocation will be blinded.

6.4.1 Study Drug Supply

Patient drug packs will be prepared by Victoria Pharmaceuticals (Boucher Crescent, Belfast, UK). Simvastatin 40mg or identical placebo tablets will be packaged in a white opaque HDPE plastic container which will be sealed with a tamper-evident seal and labelled in compliance with applicable requlatory requirements. Each container will contain 70 tablets of study drug for the treatment of one patient for 28 days (plus 7 days overage). All trial drugs will be packaged identically and identified only by the unique trial identifier.

Drug packs will be stored by Victoria Pharmaceuticals and dispatched by them to participating hospital pharmacies under the instruction of the trial manager who will be monitoring recruitment at participating sites. Hospital pharmacies will ensure that all study drugs are stored in a secured area separately from normal hospital stock under manufacturer's recommended storage conditions.

6.4.2 Study Drug Storage

The study drug should be stored below 30^{o}C..

6.4.3 Study Drug Dispensing

When a patient is recruited, the recruiting clinician will contact the randomisation service to obtain the unique trial identifier to be allocated to the patient. A confirmation email will be sent to the hospital pharmacy. The clinician will complete a trial prescription form detailing the unique trial identifier assigned to the patient. The hospital pharmacy will dispense the drug pack labelled with the corresponding unique trial identifier for the patient. The drug pack will contain all study drugs necessary to give a complete course of trial treatment to one patient.

6.4.4 Study Drug Administration

The first dose of study drug will be administered within 4 hours of randomisation and subsequent doses will be at 10am daily starting on the following calendar day. If for any reason a dose is not administered at the intended time, it may be administered subsequently but not more than 12 hours after the intended time of administration.

If patients receive more than a single bolus of amiodarone after randomisation the dose will be reduced to 40mg alternate dates, i.e. one tablet on alternate days for the duration of the treatment period.

6.4.5 Study Drug Termination Criteria

Study drug will be discontinued if any one of the following conditions is met, prior to the maximum treatment period (28 days from randomisation):

1. Study drug related adverse event
   a) CK > 10 times the upper limit of normal (ULN)
   b) ALT/AST > 5 times the ULN
2. Development of a clinical condition requiring immediate treatment with a statin
3. Discharge from critical care environment
4. Death
5. Discontinuation of active medical treatment
6. Patient or relative request for withdrawal of patient from the study
7. Decision by the attending clinician that the study drug should be discontinued on safety grounds

6.4.6 Study Drug Treatment Compliance

Nursing staff at the site will administer the study drug. Any omission of study drug will be recorded in the Case Report Form (CRF) to monitor treatment compliance. As an additional confirmation of compliance, day 7 simvastatin and its main active metabolite simvastatin acid will be measured in stored plasma after the study is complete.

6.4.7 Study Drug Accountability

Hospital pharmacies will maintain accurate and adequate records including dates of receipt, lot numbers/expiry date, quantities of drug shipments as well as dates and amounts of study drug dispensed and returned. At the end of the study, unallocated, unused and used study drug will be destroyed at site, with permission from the Sponsors and in accordance with site pharmacy procedure for destruction of IMP and hospital waste management policies. A record of the destruction will be maintained.

6.4.8 Clinical Management of Patients in the Trial

Patients involved in the trial will be managed according to best practice established locally on each unit.

6.4.8.1 Standardised ventilatory, fluid management and weaning

Clinicians will be encouraged to use a low tidal volume strategy of ventilation based on ideal body weight, a conservative fluid management protocol and a standardised weaning strategy. Rescue therapies such as high frequency oscillatory ventilation, nitric oxide and extracorporeal membrane oxygenation can be used according to local policy.

6.4.8.2 Need for statin treatment in addition to the study drug

The exclusion criteria prevent patients with ALI who have a co-existing condition that requires treatment with a statin as part of standard clinical care being recruited. In patients where there is a clinical indication for acute and immediate treatment with a statin after randomisation e.g. acute myocardial infarction, study drug will be discontinued and a statin commenced. The patient will not be unblinded and data collection will continue. This will be recorded on the CRF. Otherwise patients will not be commenced on a statin for the duration of the clinical trial. In a survey of patients admitted to ARDS Network ICUs in the US less than 1% of patients had a statin commenced during their ICU stay (personal communication; J Truwit ARDS Network investigator).

6.4.9 Study Procedures for Unblinding

As a placebo controlled, double-blind trial, patients, clinicians and PI will be blinded to each patient's allocation. All trial drugs, whether simvastatin or placebo, will be packaged identically and identified only by a unique trial identifier. Any PI may request emergency unblinding on grounds of safety. Emergency unblinding will be performed by telephone contact with the randomisation service. This option may be used only if the patient's future treatment requires knowledge of the treatment assignment. If a PI decides that there is justification to unblind a patient, they should make every attempt to contact the CTU, who will arrange for them to discuss the necessity of unblinding with a clinical member of the trial team.

6.5 Trial Assessments

All patients must be evaluated during the study according to the schedule of assessments outlined in Table 2.

Table 2: Schedule of Assessments

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8-28	Day 14	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		
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

6.5.1 Blood and Urine Sampling (Mechanisms)

Blood and urine will be taken at baseline prior to study drug administration (day 1) and on day 3, 7, 14 and 28 from all patients. Plasma from 20ml of heparinised blood along with aliquots of urine will be stored at –20^{O}C initially at the local site, and then at –70^{O}C until analysis at the Respiratory Research Laboratory at the Queen's University of Belfast (QUB). Ten ml of blood will also be collected on each patient in EDTA for genetic testing. Peripheral blood NFκB activation will be measured in 20 patients recruited at the Royal Hospitals Belfast site only. Heparinised blood (10ml) will be collected at baseline prior to study drug administration (day 1) and on days 3 and 7. Blood and urine will be stored beyond study completion for additional biomarker studies pending additional ethical approval. Samples will be labelled with the patient's unique trial identifier.

6.6 Data Collection

To ensure accurate, complete and reliable data are collected the CTU will provide training to site staff in the format of investigator meetings and/or site initiation visits. The CTU will provide the PI and research staff with training on Good Clinical Practice (GCP), the protocol, completion of the CRF and trial procedures including standard operating procedures (SOPs).

6.6.1 Recording of Data

All data for an individual patient will be collected by each PI or their delegated nominees and recorded in the CRF for the study. For the economic evaluation HRQoL will be measured using the EQ-5D administered at discharge, 3, 6 and 12 months. Resource utilisation data will be collected via questionnaires administered at 6 and 12 months.

Patient identification on the CRF and questionnaires will be through their unique trial identifier allocated at the time of randomisation and patient initials. Data will be collected and recorded on the CRF and questionnaires by site research team from the time the patient is considered for entry into the trial through to their discharge from hospital. In the event that a patient is transferred to another hospital, the site research team will liaise with the receiving hospital to ensure complete data collection.

The CRF for the study will be 2-part non-carbon required forms. CRFs and questionnaires are to be submitted to the CTU as per the CRF Submission Schedule, along with a CRF Tracking Form. The top copy of each page within the CRF will be returned to the CTU and the bottom copy will be retained at the participating site.

6.6.1.1 Follow-up at 3, 6, and 12 months

All survivors will be followed up at 3, 6, and 12 months after randomisation. HRQoL will be measured using the EQ-5D administered at discharge and at 3, 6 and 12 months. Resource utilisation data will be collected via questionnaires administered at 6 and 12 months. Where the patient has been discharged from hospital, questionnaires will be administered postally or by telephone. The participating site will provide the trial manager at the CTU with the name, address and contact details for the patient.

Trial patients will be asked to let the CTU know if they move house at any time after hospital discharge. If questionnaires are not returned telephone contact will be made to the trial patient to check that the questionnaire has been received and the patient is happy to complete it, followed by a second copy of the questionnaire. If the second questionnaire is not returned the patient will be contacted by telephone and the outcome data collected over the telephone.

6.7 Data Management

Following the submission of CRFs to the CTU, the data will be processed as per the CTU SOPs. Data queries will be generated for the investigational site as required to clarify data or request missing information. The designated site staff will be required to respond to these queries and send them back to the CTU after they have been reviewed and signed by the PI / delegated staff member. Any amended information will then be entered in the database. A copy of the signed query form should be retained with the CRF at the investigator site.

6.8 End of Trial

The trial will end when 540 patients have been recruited and completed up to twelve months of follow-up.

The trial will be stopped prematurely if:

- Mandated by the Research Ethics Committee
- Mandated by the Medicines and Healthcare products Regulatory Agency (MHRA) or the Irish Medicines Board (IMB)
- Mandated by the Sponsors (e.g. following recommendations from the Data Monitoring and Ethics Committee (DMEC))
- Funding for the trial ceases

The Research Ethics Committees that originally gave a favourable opinion of the trial, the MHRA and IMB that issued the Clinical Trial Authorisations (CTA) will be notified in writing once the trial has been concluded or if terminated early.

7 PHARMACOVIGILANCE

Timely, accurate and complete reporting and analysis of safety information from clinical trials is crucial for the protection of patients and are mandated by regulatory agencies.

7.1 Definition of Adverse Events

The EU Clinical Trials Directive 2001/20 provides the definitions in Table 3.

Table 3: Terms and Definitions for Adverse Events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
Adverse Reaction (AR)	All untoward and unintended responses to an investigational medicinal product related to any dose administered
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product).
Serious Adverse Event (SAE) **Serious Adverse Reaction (SAR)** **Suspected Unexpected Serious Adverse Reaction (SUSAR)**	Respectively, any adverse event, adverse reaction or unexpected adverse reaction that: a) results in death; b) is life-threatening; c) requires hospitalisation or prolongation of existing hospitalisation; d) results in persistent or significant disability or incapacity; e) is a congenital anomaly or birth defect; f) is any other important medical event(s) that carries a real, not hypothetical, risk of one of the outcomes above

7.2 Assessment of Causality

Each AE should be clinically assessed for causality based on the information available, i.e. the relationship of the AE to the study drug. For the purposes of this trial the causality should be assessed using the categories presented below. Drug related AEs are defined as those considered by the PI to have a possible, probable or definite relationship to the study drug. The PI at each site will evaluate all AE's for causality using the following guide:

- Unrelated – clinical event with an incompatible time relationship to study drug administration, and that could be explained by underlying disease, or other drugs or chemicals
- Unlikely – clinical event whose time relationship to study drug administration makes a causal connection improbable, but that could plausibly be explained by underlying disease or other drugs or chemicals
- Possible – clinical event with reasonable time relationship to study drug administration, but that could also be explained by concurrent disease or other drugs or chemicals
- Probable – clinical event with a reasonable time relationship to study drug administration, and is unlikely to be attributed to concurrent disease or other drugs or chemicals
- Definite – clinical event with plausible time relationship to study drug administration, and that cannot be explained by concurrent disease or other drugs or chemicals

7.3 Adverse Event Reporting Period

The AE reporting period for this trial begins upon enrolment into the trial and ends 30 days following the administration of the study drug. All AEs assessed by the PI as possibly related to the study drug and all SAEs that occur during this time will be followed until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

7.4 Adverse Event Reporting Requirements

AEs should be reported and documented on the relevant pages of the CRF, in accordance with the procedures outlined below. The PI at each site will also evaluate all AEs for expectedness in addition to causality.

7.4.1 Adverse Event Reporting

Because HARP-2 is recruiting a population that is already in a life-threatening situation, it is expected that many of the participants will experience AEs. Events that are expected in this population (i.e. events that are in keeping with the patient's underlying medical condition) should not be reported as AEs.
An adverse reaction (AR) is an AE which is related to the administration of the study drug. If any AEs are related to the study drug (i.e. are ARs) they must be reported on the AE form within the CRF.

The following are ARs which are expected and must be reported on the AE form within the CRF:

- CK >10 times the upper limit of normal
- ALT/AST >5 times the upper limit of normal

An unexpected adverse reaction (UAR) is an AE which is related to the administration of the study drug and that is unexpected, in that it has not been previously reported in the current Summary of Product Characteristics (SPC). All UARs must be reported on the AE form within the CRF.

These events will be included as part of the safety analysis for the trial and do not need to be reported separately to the CTU.

7.4.2 Serious Adverse Event Reporting

A SAE is defined as an AE that fulfils one or more of the criteria for severity outlined in Table 3.

Because HARP-2 is recruiting a population that is already in a life-threatening situation, it is expected that many of the participants will experience SAEs. Events that are expected in this population (i.e. events that are in keeping with the patient's underlying medical condition) and that are collected as outcomes of the trial, including death and organ failure should not be reported as SAEs. Other SAEs must be reported. A serious adverse reaction (SAR) is an SAE which is related to the administration of the study drug. If any of the above are related to the study drug (i.e. are SARs) they must be reported to the CTU.

The following SAR is expected and must be reported on the SAE form within the CRF.

- Need for renal replacement therapy in patients with CK > 10 times the upper limit of normal

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are considered to be caused by the study drug and are unexpected i.e. their nature or severity is not consistent with the SPC.

If a SAE occurs, reporting will follow the regulatory requirements as appropriate and all SUSARs will be the subject of expedited reporting. SAEs will be evaluated by the PI for causality (i.e. their relationship to study drug) and expectedness. SAEs will be reported using the SAE form in the patient's CRF and must be reported to the CTU within 24 hours of becoming aware of the event. The PI should not wait until all information about the event is available before notifying the CTU of the SAE. The CTU will acknowledge receipt of the SAE form within one business day by fax or email to the site. Information not available at the time of the initial report must be documented on a follow up SAE form. Follow up information should be sought and submitted as it becomes available. The follow up information should describe whether the event has resolved or persists, if and how it was treated and

whether the patient continues on the study or has been withdrawn from treatment.

NOTE: All SAEs should also be documented on the AE form within the CRF.

The CTU is responsible for reporting SAEs to the Sponsors, ethics committee, MHRA and IMB within the required timelines as per the regulatory requirements. The CTU will ensure that all relevant information about a SUSAR that is fatal or life threatening is reported to the relevant competent authorities and ethics within 7 days after knowledge of such an event and that all relevant information is communicated within an additional 8 days. All other SUSARs will be reported to the relevant competent authorities and research ethics committees within 15 days after the knowledge of such an event.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size

The mean (standard deviation; SD) VFDs in 432 patients with ALI was 12.7 (10.6) days [38].

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 [19]. Our observational data showed a 37% relative improvement in mortality in patients who received a statin [5].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% [20]. 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 [35]. In addition in a study of 2 different ventilatory strategies a reduction of 4 VFDs was achieved [39]. 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 [37]. 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 [36, 39, 40]. 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 2 groups to examine treatment effects. In keeping with recommendations on interim sample size review [41], 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.

8.2 Data Analysis

Standard approaches will be used to detect patterns in missing data. Analyses will be on an intention-to-treat basis. As VFDs are unlikely to be normally distributed, the groups will be analyzed by comparing the medians and 95% confidence intervals (CI). 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 outcomes will be analysed by survival methods and reported as hazard ratios with 95% CI. Correlations between changes in the biological markers measured and physiological and clinical outcomes will assessed by appropriate graphical and statistical methods including Chi-square and Pearson's correlation coefficient.

A detailed Statistical Analysis Plan (SAP) will be written by the trial statistician and approved by the DMEC before the end of the trial.

8.2.1 Subgroup Analysis

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 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

9 HEALTH ECONOMIC EVALUATION

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) [42] 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 [43]. 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.

Parameter uncertainty will be addressed using probabilistic sensitivity analysis. Outputs from the analysis will include the expected incremental cost effectiveness ratio (ICER), a scatter plot on the cost effectiveness plane, cost effectiveness acceptability curve (CEAC) and incremental net benefit (INB) assuming a societal willingness-to-pay of £20,000/QALY or the Republic of Ireland (ROI) equivalent.

10 REGULATIONS, ETHICS and GOVERNANCE

The trial will comply with the principles of GCP, the requirements and standards set out by the EU Directive 2001/20/EC and the applicable regulatory requirements in the UK, the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments and the Research Governance Framework and in Ireland, the European Communities (Clinical Trials on Medicinal Products For Human Use) Regulations, 2004 and subsequent amendments.

10.1 Sponsorship

The Belfast Health and Social Care Trust (BHSCT) will act as Sponsor for UK study sites and the National University of Ireland (NUI) Galway will act as Sponsor for Irish study sites. Each of the Sponsors will therefore only have

responsibility for the conduct of the study at sites in each of their respective jurisdictions.

Separate agreements will be put in place between each of the Sponsors and individual participating sites within their respective jurisdictions. The Chief Investigator (CI) in the UK and the CI in Ireland will take overall responsibility for the conduct of the trial in each of their own jurisdictions.

Separate agreements will be put in place between each of the Sponsors and the Clinical Research Support Centre (CRSC), the trials co-ordinating centre, who will undertake delegated Sponsor duties in relation to the management of this study.

In addition the PI at each site must agree to the Terms and Conditions of participation in the trial before the study starts at that site.

10.2 Regulatory and Ethical Approvals

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The protocol will be approved by a Multi-Centre Research Ethics Committee (MREC) for UK sites and by a recognised Research Ethic Committees (REC) for sites located in Ireland.

The trial will be conducted in accordance with the EU Directive 2001/20/EC and adhere to the appropriate regulatory requirements in each jurisdiction. A CTA will be obtained from the MHRA and IMB before the start of the trial.

The trial will be registered with the International Standard Randomised Controlled Trial Number (ISRCTN) register and the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database.

The trial has been registered with the UK National Institute for Health Research (NIHR) Clinical Research Portfolio. In order that the trial remains on the NIHR Portfolio and receives the appropriate level of support through the relevant Local Research Network, accrual data on patient recruitment will be forwarded to the UK Clinical Research Network (UKCRN) Co-ordinating Centre on a monthly basis by the CTU.

10.3 Ethical Considerations

The vulnerability of this study group is fully appreciated and every effort will be undertaken to protect their safety and well-being. In line with the applicable regulatory requirements and to comply with the Research Governance Framework, consenting processes will be standardised and a robust SOP for consenting participants will be adhered to.

10.4 Protocol Compliance

The investigators will conduct the study in compliance with the protocol given approval/favourable opinion by the Ethics Committee and the appropriate regulatory authority. Changes to the protocol will require competent

authority/ethics committee approval/favourable opinion prior to implementation, except when modification is needed to eliminate an immediate hazard(s) to patients. The CTU in collaboration with the Sponsors will submit all protocol modifications to the competent authority/research ethics committees for review in accordance with the governing regulations. Protocol compliance will be monitored by the trial manager who will undertake site visits to ensure that the trial protocol is adhered to and that necessary paperwork (CRF's, patient consent) are being completed appropriately. Any deviations from the protocol will be fully documented in source documentation and in the CRF.

10.5 Patient Confidentiality

In order to maintain confidentiality, all CRFs, questionnaires, study reports and communication regarding the study will identify the patients by the assigned unique trial identifier and initials only. Patient confidentiality will be maintained at every stage and will not be made publicly available to the extent permitted by the applicable laws and regulations.

10.6 Good Clinical Practice

The trial will be carried out in accordance with the principles of the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines (www.ich.org). The CTU will provide training to PI and research staff on GCP.

10.7 Trial Monitoring

10.7.1 Direct Access to Data

The agreement with each PI will include permission for trial related monitoring, audits, ethics committee review and regulatory inspections, by providing direct access to source data and trial related documentation. Consent from patients/legal representatives for direct access to data will also be obtained. The patients' confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

10.7.2 Monitoring Arrangements

The CTU will be responsible for trial monitoring. On-site monitoring visits will be conducted in accordance with the study monitoring plan. On-site monitoring will be an ongoing activity from the time of initiation until study close-out and will comply with the principles of GCP and EU directive 2001/20/EC. The frequency and type of monitoring will be detailed in the monitoring plan and agreed by the trial Sponsors.

Before the study starts at a participating site, an initiation visit will take place to ensure that all relevant essential documents and trial supplies are in place and that site staff are fully aware of the study protocol and SOPs. On site monitoring visits during the study, will check the completeness of patient records, the accuracy of entries on CRFs, the adherence to the protocol,

SOPs and GCP, and the progress of patient recruitment. Monitoring will also ensure that the study drug is being stored, dispensed and accounted for according to specifications.

The PI should ensure that access to all trial related documents including source documents (to confirm their consistency with CRF entries) are available during monitoring visits. The extent of source data verification (SDV) will be documented in the monitoring plan.

10.8 Indemnity

The BHSCT will provide indemnity for any negligent harm caused to patients by the design of the research protocol for UK study sites through the Clinical Negligence Fund in Northern Ireland. In Ireland, the State Claims Agency, Clinical Indemnity Scheme, will provide clinical indemnity for any harm caused to patients by the design of the research protocol. Additionally, indemnity to allow for no-fault compensation will be provided for by NUI Galway for Irish sites. The Agreements put in place between the Sponsors and individual participating sites will cover the indemnity provision for negligent harm.

10.9 Finance

The study is funded by the Efficacy and Mechanism Evaluation (EME) programme, which is funded by the Medical Research Council (MRC) and managed by the NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton.

10.10 Record Retention

The PI will be provided with an ISF by the CTU and will maintain all trial records according to GCP and the applicable regulatory requirements. The trial master file (TMF) will be held by the CTU within the BHSCT and the essential documents that make up the file will be listed in an SOP. On completion of the trial the TMF and study data will be archived by the CTU according to the applicable regulatory requirements and for up to 15 years as required by the BHSCT and NUI Galway as Sponsors. Following confirmation from the Sponsors the CTU will notify the PI when they are no longer required to maintain the files. If the PI withdraws from the responsibility of keeping the trial records, custody must be transferred to a person willing to accept responsibility and this must be documented in writing to the CTU.

11 TRIAL COMMITTEES

11.1 Trial Management Arrangements

The Chief Investigators will have overall responsibility for the conduct of the study. The CRSC CTU will be the Trial Co-ordinating Centre. The CTU will provide trial management and coordination, data management, monitoring, health economics and statistical services. The trial manager will be responsible on a day to day basis for overseeing and co-ordinating the work of the multi-disciplinary trial team, and will be the main contact between the

trial team (section 2) and PI and research staff at participating sites. The CTU will assist and facilitate the setting up of sites wishing to collaborate in the trial which will include:

- Arranging site initiation visits and providing training to site staff
- Development and distribution of the case report form and questionnaires
- Organisation of a telephone randomisation service for patient registration on the trial
- Monitor the collection of data, process data and conduct data validation

11.2 Trial Management Group

A Trial Management Group (TMG) will be established and chaired by the trial manager, and will have representation on it from the CTU, the CI in the UK, the CI in Ireland and Sponsors (as required). This group will have responsibility for the day to day operational management of the trial, and regular meetings of the TMG will be held to discuss and solve problems and monitor progress. The discussions of the TMG will be formally minuted and a record kept in the TMF.

11.3 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. Membership of the TSC is listed in section 11.3.1 and representatives of the trial Sponsors and Funder will be invited to all TSC meetings. 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.

11.3.1 Trial Steering Committee Membership

Membership of the TSC will include:

Dr Duncan Young (Chair), Senior Clinical Lecturer in Intensive Care, University of Oxford.

Dr Rupert Pearse, Senior Lecturer & Consultant in Intensive Care Medicine, Barts and The London School of Medicine and Dentistry.

Professor Kathy Rowan, Director, Intensive Care National Audit & Research Centre, London.

Mr Barry Williams, Chairman of the Critical Care Patient Liaison Committee (CritPaL), The Intensive Care Society, London.

Professor Danny McAuley (Chief Investigator for UK), Professor/Consultant. Centre for Infection and Immunity, Queen's University Belfast.

Professor John Laffey (Chief Investigator for Ireland), Professor and Head of Department, Department of Anaesthesia and Intensive Care, Clinical Science Institute, National University of Ireland Galway.

Ms Lynn Murphy, Quality Assurance Manager, Clinical Research Support Centre, Clinical Trials Unit, Belfast.

Observers may be invited and be in attendance at TSC meetings, such as the Sponsor or Funder representatives or the trial manager to provide input on behalf of the CTU.

11.4 Data Monitoring and Ethics Committee

A DMEC will be appointed comprising two clinicians with experience in undertaking clinical trials / caring for critically ill patients and a statistician who are independent of the trial. Membership of the DMEC is listed in section 11.4.1 and biannual meetings will be 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 will monitor recruitment, adverse events and outcome data.

During the recruitment period, reports will be provided to the DMEC which will 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.

11.4.1 Data Monitoring and Ethics Committee Membership

Membership of the DMEC will include:

Dr Geoff Bellingan (Chair), Clinical Director of Bloomsbury Institute of Intensive Care Medicine, University College of London Hospitals National Health Service (NHS) Foundation Trust, London.

Dr David Harrison, Senior Statistician, Intensive Care National Audit & Research Centre, London.

Dr Anthony Gordon, Consultant & Honorary Senior Lecturer, Critical Care Medicine, Charing Cross Hospital Imperial College NHS Trust, London.

11.5 User Involvement

The study will be registered with the INVOLVE open-access database which registers research health care projects involving members of the public as partners in the research process (http://www.involve.org.uk). Patient experience whilst critically ill will be taken into consideration when preparing patient information leaflets and consent forms. The Chairman of CritPaL (Barry Williams) will represent the patient's perspective on the TSC ensuring that the trial remains considerate of the needs of the patients and their families.

12 PROPOSED TRIAL MILESTONES

The trial will be carried out over 4 years. There will be a 3 month run-in period to allow regulatory applications, set-up and training. Patient recruitment has conservatively been estimated at 1.3 patients/site/month over 31 months. There will be 12 months of follow up to collect HRQoL outcomes. Data cleaning and validation, analysis of the primary and other physiological outcomes, laboratory assays and analyses, and publication of these results will also be undertaken during this 12 month period. A final 2-month period is required for analysis and publication of the follow-up results. Trial milestones are detailed in the project GANTT chart shown in Table 4.

Table 4: Trial Milestones

Year	1				2				3				4			
Quarter	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Management meetings	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Steering committee	x		x				x				x				x	
DMEC	x		x				x				x				x	
Trial set up	x															
Patient recruitment		x	x	x	x	X	x	x	x	x	x	x				
Patient accrual		36	90	144	198	252	306	360	414	468	522	540				
HRQoL follow-up			x	x	x	X	x	x	x	x	x	x	x	x	x	
Data entry			x	x	x	X	x	x	x	x	x	x	x	x	x	
QA and monitoring		x	x	x	x	X	x	x	x	x	x	x	x	x	x	
Laboratory analysis													x	x	x	
HE analysis															x	x
Data analysis													x	x	x	x
Trial Report															x	x
Trial close down																x
Dissemination													x			x

13 DISSEMINATION

The success of the trial depends on the collaboration of doctors, nurses and researchers from across the study sites. Therefore the results of the trial will be reported first to trial collaborators. The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org).

The findings will be presented at national and international meetings with open access abstracts on-line e.g. the American Thoracic Society annual meeting, and in accordance with the open access policies proposed by the leading research funding bodies we aim to publish the findings in high quality peer-reviewed open access (via Pubmed) journals. This will secure a searchable compendium of these publications and make the results readily accessible to the public, health care professionals and scientists.

Due to limited resources, it will be not be possible to provide each surviving patient with a personal copy of the results of the trial. However a lay person's summary of the principal findings of the results will be sent to all patients involved in the study at their request. In addition a lay person's summary will be sent to local and national patient support and liaison groups (e.g. CritPaL, hospital patient groups). A report of the study findings will be sent to the INVOLVE registry. Where appropriate, research details will also be posted on institutional websites available to the general public. In addition, the most significant results will be communicated to the public through press releases.

14 LIST OF APPENDICES

Appendix 1	Child-Pugh Classification

(From Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R (1973). Transection of the oesophagus for bleeding oesophageal varices. *The British Journal of Surgery* **60** (8): 646–9.)

The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.

		Points scored		
		1	**2**	**3**
Serum bilirubin µmol/l		<35	35-50	>50
Serum albumin g/l		>35	28-35	<28
Ascites		None	Slight	Moderate
Encephalopathy		None	Grade 1-2	Grade 3-4
Coagulation	PT secs. prolonged	1-4	4-10	>10
	INR	<1.7	1.71-2.20	> 2.20

Encephalopathy grades are scored as follows:

Grade 1 - Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired performance of addition.
Grade 2 - Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior; impaired performance of subtraction
Grade 3 - Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation
Grade 4 - Coma (unresponsive to verbal or noxious stimuli).

Appendix 2	References

[1] Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, et al. Incidence and outcomes of acute lung injury. The New England Journal of Medicine. 2005;353(16):1685-93.

[2] Brun-Buisson C, Minelli C, Bertolini G, Brazzi L, Pimentel J, Lewandowski K, et al. Epidemiology and outcome of acute lung injury in European intensive care units. Results from the ALIVE study. Intensive Care Medicine. 2004;30(1):51-61.

[3] Dowdy DW, Eid MP, Dennison CR, Mendez-Tellez PA, Herridge MS, Guallar E, et al. Quality of life after acute respiratory distress syndrome: a meta-analysis. Intensive Care Medicine. 2006 Aug;32(8):1115-24.

[4] Rossi C, Simini B, Brazzi L, Rossi G, Radrizzani D, Iapichino G, et al. Variable costs of ICU patients: a multicenter prospective study. Intensive Care Medicine. 2006;32(4):545-52.

[5] Irish Critical Care Trials Group. Acute lung injury and the acute respiratory distress syndrome in Ireland: a prospective audit of epidemiology and management. Critical Care. 2008;12(1):R30.

[6] Cheung AM, Tansey CM, Tomlinson G, Diaz-Granados N, Matte A, Barr A, et al. Two-year outcomes, health care use, and costs of survivors of acute respiratory distress syndrome. American Journal of Respiratory and Critical Care Medicine. 2006;174(5):538-44.

[7] Ware LB, Matthay MA. The acute respiratory distress syndrome. The New England Journal of Medicine. 2000;342(18):1334-49.

[8] Modelska K, Pittet JF, Folkesson HG, Courtney Broaddus V, Matthay MA. Acid-induced lung injury. Protective effect of anti-interleukin-8 pretreatment on alveolar epithelial barrier function in rabbits. American Journal of Respiratory and Critical Care Medicine. 1999;160(5 Pt 1):1450-6.

[9] Craig T, O'Kane CM, McAuley DF. Potential mechanisms by which statins modulate pathogenic mechanisms important in the development of acute lung injury. In: Vincent JL, ed. *27th Yearbook of Intensive Care and Emergency Medicine*. Berlin: Springer-Verlag 2007.

[10] Frank JA, Parsons PE, Matthay MA. Pathogenetic significance of biological markers of ventilator-associated lung injury in experimental and clinical studies. Chest. 2006;130(6):1906-14.

[11] Monchi M, Bellenfant F, Cariou A, Joly LM, Thebert D, Laurent I, et al. Early predictive factors of survival in the acute respiratory distress syndrome. A multivariate analysis. American Journal of Respiratory and Critical Care Medicine. 1998;158(4):1076-81.

[12] Liappis AP, Kan VL, Rochester CG, Simon GL. The effect of statins on mortality in patients with bacteremia. Clinical Infectious Diseases. 2001;33(8):1352-7.

[13] Almog Y, Shefer A, Novack V, Maimon N, Barski L, Eizinger M, et al. Prior statin therapy is associated with a decreased rate of severe sepsis. Circulation. 2004 Aug 17;110(7):880-5.

[14] Hackam DG, Mamdani M, Li P, Redelmeier DA. Statins and sepsis in patients with cardiovascular disease: a population-based cohort analysis. Lancet. 2006;367(9508):413-8.

[15] Kruger P, Fitzsimmons K, Cook D, Jones M, Nimmo G. Statin therapy is associated with fewer deaths in patients with bacteraemia. Intensive Care Medicine. 2006;32(1):75-9.

[16] Thomsen RW, Riis A, Kornum JB, Christensen S, Johnsen SP, Sorensen HT. Preadmission use of statins and outcomes after hospitalization with pneumonia: population-based cohort study of 29,900 patients. Archives of Internal Medicine. 2008;168(19):2081-7.
[17] Chalmers JD, Singanayagam A, Murray MP, Hill AT. Prior Statin Use Is Associated with Improved Outcomes in Community-acquired Pneumonia. The American Journal of Medicine. 2008;121(11):1002-7.e1.
[18] Mortensen EM, Restrepo MI, Anzueto A, Pugh J. The effect of prior statin use on 30-day mortality for patients hospitalized with community-acquired pneumonia. Respiratory Research. 2005;6:82.
[19] Kor DJ, Iscimen R, Yilmaz M, Brown MJ, Brown DR, Gajic O. Statin administration did not influence the progression of lung injury or associated organ failures in a cohort of patients with acute lung injury. Intensive Care Medicine. 2009;35:1039-1046.
[20] Shyamsundar M, McKeown S, O'Kane C, Craig T, Brown V, Thickett DR, et al. Simvastatin decreases lipopolysaccharide-induced pulmonary inflammation in healthy volunteers. American Journal of Respiratory and Critical Care Medicine. 2009;179:1107-14.
[21] Steiner S, Speidl WS, Pleiner J, Seidinger D, Zorn G, Kaun C, et al. Simvastatin blunts endotoxin-induced tissue factor in vivo. Circulation. 2005;111(14):1841-6.
[22] Novack V, Eisinger M, Frenkel A, Terblanche M, Adhikari NK, Douvdevani A, et al. The effects of statin therapy on inflammatory cytokines in patients with bacterial infections: a randomized double-blind placebo controlled clinical trial. Intensive Care Medicine. 2009; 35:1255-1260.
[23] Choi HS, Park MJ, Kang HM, Kim YJ, Choi CW, You JH, et al. Statin use in sepsis due to pneumonia. American Journal of Respiratory and Critical Care Medicine. 2008;177:A580.
[24] Gonzalez C, Luna A, Morales M, Sanchez J, Guzman C, Granillo J. Statin anti-inflammatory therapy in septic patients. Critical Care. 2008;12(Suppl 5):P26.
[25] The A to Z Investigators. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes. JAMA. 2004;292:1307-16.
[26] Bowman L, Armitage J, Bulbulia R, Parish S, Collins R. Study of the effectiveness of additional reductions in cholesterol and homocysteine (SEARCH): characteristics of a randomized trial among 12064 myocardial infarction survivors. American Heart Journal. 2007;154(5):815-23.
[27] Kruger PS, Freir NM, Venkatesh B, Robertson TA, Roberts MS, Jones M. A preliminary study of atorvastatin plasma concentrations in critically ill patients with sepsis. Intensive Care Medicine. 2008;35:717-721
[28] Drage SM, Simpkin AL, Neuvonen PJ, Watkinson PJ, Barber VS, Young JD. Plasma simvastatin concentrations in critically ill septic patients. Journal of the Intensive Care Society. 2009;10:61.
[29] Drage SM, Barber VS, Watkinson PJ, Young JD. Simvastatin for the treatment of severe sepsis: a randomised controlled pilot study. Journal of the Intensive Care Society. 2009;10:61.
[30] Jacobson J, R., Barnard J, W., Grigoryev D, N., Ma S, Fan, Tuder R, M., Garcia J, G.N. Simvastatin attenuates vascular leak and inflammation in murine inflammatory lung injury. American Journal of Physiology. 2005;288:L1026-32.

[31] Shah AI, Sobnosky S, Shen AY, Jorgensen MB. High dose statins are associated with a reduced all cause mortality in patients hospitalized with sepsis and severe sepsis. Crit Care Med. 2009;36:pA15.
[32] Adhikari N, Burns KE, Meade MO. Pharmacologic therapies for adults with acute lung injury and acute respiratory distress syndrome. Cochrane Database Syst Rev. 2004(4):CD004477.
[33] Matthay MA, Zimmerman GA, Esmon C, Bhattacharya J, Coller B, Doerschuk CM, et al. Future research directions in acute lung injury: summary of a National Heart, Lung, and Blood Institute working group. American journal of respiratory and critical care medicine. 2003 2003/04/01/;167(7):1027-35.
[34] Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med. 1994 1994/03//;149(3 Pt 1):818-24.
[35] Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, et al. Comparison of two fluid-management strategies in acute lung injury. The New England journal of medicine. 2006 Jun 15;354(24):2564-75.
[36] Matthay MA, Brower R, Thompson BT, Schoenfeld D, Eisner MD, Carson S, et al. Randomized, placebo–controlled trial of an aerosolized beta–2 adrenergic agonist (albuterol) for the treatment of acute lung injury. American journal of respiratory and critical care medicine. 2009;179:A2166.
[37] Harvey S, Harrison DA, Singer M, Ashcroft J, Jones CM, Elbourne D, et al. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. Lancet. 2005 Aug 6-12;366(9484):472-7.
[38] The ARDS Network investigators. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. New England Journal of Medicine. 2000;342(18):1301-8.
[39] Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl JL, et al. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. Jama. 2008 Feb 13;299(6):646-55.
[40] Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. The New England journal of medicine. 2004 Jul 22;351(4):327-36.
[41] Machin D, Campbell MJ. Design of Studies for Medical Research. Chichester: Wiley 2005.
[42] Excellence NIfHaC. Guide to the methods of technology appraisal. London: NICE 2008.
[43] Curtis LA. Unit Costs of Health and Social Care 2007. Canterbury: Personal Social Services Research Unit, University of Kent 2007.