PREVENTION HARP-2

Prevention Of Post-operative Complications By Using HMG-CoA Reductase Inhibitor In Patients Undergoing One Lung Ventilation For Surgery – A multicentre, randomised, double blind, placebo controlled trial

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Chief Investigator:	Dr Murali Shyamsundar Room N2019, The Wellcome-Wolfson Building, Centre for Infection and Immunity, Health Sciences Building, Lisburn Road, Belfast BT9 7BL

PROTOCOL AUTHORISATION

Protocol Title	**Prevention Of Post-operative Complications By Using HMG-CoA Reductase Inhibitor In Patients Undergoing One Lung Ventilation For Surgery – A multicentre, randomised, double blind, placebo controlled trial**
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A review of the protocol has been completed and is understood and approved by the following:

Murali Shyamsundar		____ / ____ / ____
Chief Investigator Name	Signature	Date
Christina Campbell		____ ____ ____
Statistician	Signature	Date

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LIST OF ABBREVIATIONS

Abbreviation / Acronym	Full Wording
AAA	Abdominal Aortic Aneurysm
ACR	Albumin:creatinine ratio
AE	Adverse Event
AF	Atrial Fibrillation
ALT	Alanine Aminotransferase
Ang-I/II	Angioprotein
AR	Adverse Reaction
ARDs	Acute Respiratory Distress Syndrome
AST	Aspartate Aminotransferase
BHSCT	Belfast Health & Social Care Trust
BNF	British National Formulary
CEA	Cost-Effectiveness Analysis
CEAC	Cost-Effectiveness Acceptability Curve
CK	Creatine Kinase
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
SrCr	Serum Creatinine
CRP	C-reactive protein
CrCl	Creatinine clearance
CTA	Clinical Trial Authorisations
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
DVT/PE	Deep vein thrombosis/ pulmonary embolism
EBC	Exhaled Breath Condensate
ECG	Electrocardiograph
ECM	Pulmonary extracellular matrix
EQ-5D-5L	EuroQoL-5 Dimension Questionnaire (5 level version)
EDC	Electronic Data Capture
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
HDPE	High Density Polyethylene
HDU	High Dependency Unit
HCG	Human Chorionic Gonadotropin
HRQoL	Health Related Quality of Life
HO-1	Haemoxygenase 1
ICER	Incremental Cost-effectiveness Ratio
IB	Investigator Brochure
ICCTG	Irish Critical Care Trials Group
ICH	International Conference of Harmonisation
ICS	Intensive Care Society
ICU	Intensive Care Unit
IL-1β	Interleukin-1β
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number Register
IU/L	International Units/ Litre
KDIGO	Kidney Disease Improving Global Outcomes
LPS	Inhaled lipopolysaccharide

MDM	Multi-Disciplinary Meeting
MGS	Melbourne Group Scale
MHRA	Medicine and Healthcare Products Regulatory Agency
MI	Myocardial Infarction
MINS	Myocardial Ischaemia post Non-cardiac Surgery
MPO	Myeloperoxidase
NCEPOD	National Confidential Enquiry into Perioperative Deaths
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICTU	Northern Ireland Clinical Trials Unit
NIHR	National Institute for Health Research
NSAIDs	Non-steroidal anti-inflammatory drugs
OLV	One-lung ventilation
QALY	Quality Adjusted Life Year
PatRel	Critical Care Patients and Relatives Committee
PPC	Postoperative Pulmonary Complications
PI	Principal Investigator
PIIINP	Procollagen peptide III
PSSRU	Personal Social Services Research Unit
RAGE	Receptor for Advanced Glycation End-Products
REC	Research Ethics Committee
ROS	Reactive Oxygen Species
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
sICAM	Soluble Intercellular Adhesion Molecule
SmPC	Summary of Product Characteristics
SOPs	Standard Operating Procedures
SOFA	Sequential Organ Failure Assessment score
SP-D	Surfactant Protein-D
SUSARs	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TNFα	Tumour necrosis factor α
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
VFDs	Ventilator free days
vWF	von Willlebrand

1. STUDY SUMMARY

Scientific title	**Prevention Of Post-operative Complications By Using HMG-CoA Reductase Inhibitor In Patients Undergoing One Lung Ventilation For Surgery – A multicentre, randomised, double blind, placebo controlled trial**
Public title	Prevention of heart and lung complications by using simvastatin in patients undergoing surgery.
Health condition(s) or problem(s) studied	Cardiac and respiratory complications after elective oesophagectomy, lobectomy or pneumonectomy
Study Design	(i) Type of study - interventional (ii) Study design including: - Randomised - Placebo controlled - Parallel - Purpose - Prevention - Phase II
Study Aim and Objectives	The aim of this study is to test the hypothesis that treatment with enteral simvastatin 80mg once daily for four days pre-surgery and up to 7 days post-surgery will prevent the development of cardiac and respiratory complications in patients undergoing one lung ventilation for elective oesophagectomy, lobectomy or pneumonectomy
Study Intervention	(i) Simvastatin 80mg once daily (ii) Control – Placebo once daily
Primary Outcome	Composite endpoint of postoperative pulmonary complications (PPC), acute respiratory distress syndrome (ARDS) and myocardial infarction (MI). ARDS defined according to the Berlin definition, PPC as defined by Melbourne group scale (MGS) and cardiac ischaemia as defined by ischaemic chest pain, electrocardiograph (ECG) changes and a raise in plasma troponin and also by myocardial ischaemia post non-cardiac surgery (MINS) criteria by day 7 post surgery, or discharge if prior to day 7.
Key Secondary Outcomes	**<u>Clinical Outcomes</u>** 1. Mortality at day 28 and 90 2. Ventilator free days (VFDs) 3. ARDS, PPC and MI within 28 days of surgery or hospital discharge if earlier 4. Atrial fibrillation (AF) within 28 days of surgery or hospital discharge if earlier 5. Venous thromboembolism within 28 days of surgery or hospital discharge if earlier

	6. Incidence and nature of any surgical complications will be recorded 7. ARDS within 7 days of surgery or hospital discharge if earlier. 8. PPC within 7 days of surgery or hospital discharge if earlier. 9. MI within 7 days of surgery or hospital discharge if earlier. 10. MINS within 7 days of surgery or hospital discharge if earlier **Safety** 1. Creatine Kinase IU/L (CK) >10 times the upper limit of normal (day of surgery, day 3, day 7 post-surgery) of local laboratory range 2. Alanine Aminotransferase / Aspartate Aminotransferase IU/L (ALT/AST) > 5 times the upper limit of normal (day of surgery, day 3, day 7 post-surgery) of local laboratory range 3. Acute kidney injury defined according to KDIGO guidelines (using change from baseline serum creatinine) within seven days of surgery 4. Adverse events (AEs), Serious adverse events (SAEs) and occurrence of suspected unexpected serious adverse reactions (SUSARs) as defined in section 11.10.1 **Health Economic Outcomes** 1. Health related quality of life (HRQoL): • EuroQoL-5 Dimension Questionnaire (5 level version) at baseline and 90 days post-surgery 2. Resource use: • Length of Intensive Care Unit (ICU) stay (level 3 care) • Length of High Dependency Unit (HDU) stay (level 2 care) • Total length of hospital stay • Health service contacts up to 90 days post-surgery

Key Inclusion and Exclusion Criteria	**Inclusion criteria** 1. Adult patients ≥18 years of age undergoing one lung ventilation for elective oesophagectomy, lobectomy or pneumonectomy will be eligible for inclusion in the study. 2. Female subjects must be surgically sterile, or be postmenopausal, or must agree to use effective contraception during the period of the trial and for at least 30 days after completion of treatment. A pregnancy test measured by urine Human Chorionic Gonadotropin (HCG) in females with child bearing potential will be performed at pre-operative assessment clinic **Exclusion criteria** 1. Age < 18 years 2. Known active liver disease (Child's Pugh score > 11) or abnormal liver function tests i.e. transaminases (AST or ALT) > 3 times upper limit normal range in the local laboratory 3. Renal impairment (calculated creatinine clearance less than 30mL/minute) 4. Inability to take oral medication pre-operatively 5. Subject reported lactose intolerance 6. Participation in other intervention trials within 30 days. 7. Current treatment with statins 8. Known hypersensitivity to the study medication 9. Previous adverse reaction to statins 10. Concomitant use of fibrates or other lipid-lowering therapy 11. Concomitant use of itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprivir, telaprevir, nefazodone, Cobicistat cyclosporine, danazol, amiodarone, amlodipine, verapamil or diltiazem, fusidic acid and niacin. 12. Patients must be able to understand and give signed and dated informed consent indicating that they understand all the pertinent aspects of the trial prior to enrolment 13. Currently pregnant or lactating
Countries of Recruitment	UK
Study Setting	Multi-centre
Target Sample Size	452
Study Duration	45 months

2. STUDY TEAM

Chief Investigator	**Dr Murali Shyamsundar** Clinical Senior Lecturer Room N02019, The Wellcome-Wolfson Building Centre for Infection and Immunity Queen's University of Belfast Lisburn Road Belfast, BT9 7BL
Co-Investigators	**Prof Danny McAuley** Clinical Professor (Cons) (JA) Room S02057, The Wellcome-Wolfson Building Centre for Infection and Immunity Queen's University of Belfast Lisburn Road Belfast, BT9 7BL **Dr Cecilia O'Kane** Clinical Senior Lecturer Room N02018, The Wellcome-Wolfson Building Centre for Infection and Immunity Queen's University of Belfast Lisburn Road Belfast, BT9 7BL **Prof Gavin D Perkins** Clinical Trials Unit Room T1.18 Warwick Clinical Trials Unit Warwick Medical School University of Warwick Coventry CV4 7AL
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Health Economist	**Dr Ashley Agus** Northern Ireland Clinical Trials Unit (NICTU) Education & Research Centre The Royal Hospitals Grosvenor Road Belfast BT12 6BN

Clinical Trials Unit	**Northern Ireland Clinical Trials Unit (NICTU)** 1st Floor Elliott Dynes Building Royal Hospitals Grosvenor Road Belfast, N. Ireland BT12 6BA
Primary Sponsor	**Belfast Health and Social Care Trust** Research Management Room 2008 2nd Floor King Edward Building Royal Hospitals Site Belfast Health and Social Care Trust Grosvenor Road Belfast BT12 6BA
Primary Sponsor's Reference	15085MS-AS
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Contact for scientific queries	**Dr Murali Shyamsundar** Clinical Senior Lecturer Room N02019, The Wellcome-Wolfson Building Centre for Infection and Immunity Queen's University of Belfast Lisburn Road Belfast, BT9 7BL

3. FUNDING

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4. ROLES AND RESPONSIBILITIES

The Chief Investigator (CI) will have overall responsibility for the conduct of the study. The Clinical Trial Unit (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), Principal Investigator (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 an automated randomisation service for patient registration on the trial
- Monitor the collection of data, process data and conduct data validation

4.1 Contributorship

Dr Murali Shyamsundar and Prof Danny McAuley conceived the study. Dr Murali Shyamsundar, Prof Danny McAuley and Dr Cecilia O'Kane are grant holders. The CTU statistician provided statistical expertise in clinical trial design and is conducting the primary statistical analysis. The CTU Health Economist provided health economics expertise in clinical trial design and is overseeing the primary health economics analysis. All authors, investigators and the Trial Management Group (TMG) contributed to the refinement of the study protocol and approved the final manuscript.

4.2 Sponsor and Funder

The Belfast Health and Social Care Trust (BHSCT) will act as Sponsor for the study and the CI will take overall responsibility for the conduct of the trial. Separate agreements will be put in place between the Sponsor, CI and each organisation who will undertake Sponsor-delegated duties in relation to the management of the study.

4.3 Committees

4.3.1 Trial Management Group (TMG)

A TMG will be established and Chaired by the CI. The TMG will have representation from the CTU and other investigators/collaborators that are involved in the study and provide trial specific expertise, for example the trial statistician. 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 monitor progress. The discussions at TMG meetings will be formally minuted and filed within the Trial Master File (TMF).

A TMG Charter will be drawn up to detail the terms of reference of the TMG including membership and roles/responsibilities.

4.3.2 Trial Steering Committee (TSC)

The TSC will oversee the progress of the trial on behalf of the trial funder and sponsor. The TSC will provide overall supervision of the trial and provide advice through the Chair to the CI, Sponsor, Funder and host institution on all appropriate aspects of the trial. The TSC will concentrate on the progress of the trial, adherence to protocol, patient safety, and new information of relevance to the research question, the rights, safety and wellbeing of trial participants and ensure that appropriate approvals are obtained in line with the project plan. The TSC will agree proposals for substantial amendments and provide advice to the sponsor and funder regarding the approval of such amendments.

Membership of the TSC will comprise of an independent chair, the CI (or designee), independent clinicians with relevant expertise, independent statisticians/epidemiologists/diagnosticians with relevant expertise and at least one patient/public representative. The TSC will meet at least annually and will have a minimum of 75% independent members. The TSC may be convened to discuss issues and recommendations raised by the Data Monitoring Ethics Committee (DMEC), in addition to the scheduled annual meetings.

A TSC charter will be drawn up to detail the terms of reference of the TSC including membership and roles/responsibilities.

4.3.3 Data Monitoring and Ethics Committee (DMEC)

The role of the DMEC is to safeguard the rights, safety and wellbeing of trial participants, monitor data and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue and monitor the overall conduct of the study to ensure the validity and integrity of the study findings.

Membership of the DMEC will be completely independent and comprise of experts in the field e.g. a clinician and statistician with relevant experience. The first DMEC meeting will take place before the study starts, after the first fifty participants have been enrolled or after 12 months of recruitment, whichever is earlier. Thereafter DMEC will meet at least annually.

A DMEC charter will be drawn up to detail the terms of reference of the DMEC including membership and roles/responsibilities. A DMEC report will be drawn up by the trial statistician to include information on any SAEs, SUSARs, AEs, recruitment, outcomes and any other data requested by the committee.

4.3.4 User Involvement or any other relevant committees

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). The Intensive Care Society (ICS) has a close working relation with a Critical Care Patients and Relatives Committee (PatRel). PatRel is led by people who have survived critical illness and their relatives. Members of the public will be involved in the management of the research through the steering/advisory group. They will also be involved in the development of participant information resources, contributing to the study report and the dissemination of research findings.

5 BACKGROUND AND RATIONALE

5.1 Background Information

One lung ventilation (OLV) is an anaesthetic technique used in common surgeries like oesophagectomy, lobectomy and pneumonectomy and is associated with postoperative pulmonary complications (PPC) [1] including acute respiratory distress syndrome (ARDS)[3]and cardiac complications[4,5]. Development of these complications is associated with a significantly worse outcome including increased mortality, readmission to ICU, increased ICU and hospital stay [1, 4, 5].

Postoperative pulmonary complications PPC and ARDS are common and devastating clinical conditions with high morbidity and mortality secondary to respiratory failure and multi-organ failure [6]. PPC and ARDS have a high incidence as well as a high mortality rate of up to 65% [6, 7]. Cardiac and respiratory complications have both immediate and long standing resource implications which include an increase in ventilator usage, critical care support and on-going rehabilitation needs in the community post discharge [5, 7-10, 11]. There is a significant reduction in health related quality of life [12, 13] and economic loss as up to 46% of survivors are still unable to work for 12 months after discharge[14].

The precise incidence of PPC and ARDS post OLV is less well defined but studies have shown a high incidence ranging from 13 – 43% [2,15-19] and a mortality rate of up to 50% has been reported. [17]. The recent national confidential enquiry into perioperative deaths (NCEPOD) has highlighted post-operative respiratory problems as the commonest cause of morbidity in patients undergoing surgeries utilising one lung ventilation technique [20]. The pathophysiology of ARDS post-surgery is similar to that of ARDS secondary to the classic injuries such as sepsis and trauma[15]. One-lung ventilation (OLV) is implicated in the aetiology of ARDS following surgery using this technique [17] and lung injury and inflammation is detectable after OLV even in the absence of clinical ARDS[21].

5.2 Rationale for the Study

There is no specific pharmacological therapy for cardiac or respiratory complications post elective surgeries utilising one lung ventilation technique. Planned surgery however allows modulation of the underlying inflammatory processes pre and post-surgery and may improve surgical outcome. A recent Cochrane review on the pharmacotherapy for ARDS concluded that the “Effective pharmacotherapy in ARDS is extremely limited, with insufficient evidence to support any specific intervention” and called for further clinical trials in this area [22]. Statins have been shown to modulate various inflammatory processes underlying cardiac and respiratory complications. This trial will study statins as a specific pharmacotherapy to prevent these complications post-surgery.

Statins can modulate mechanisms important in the pathogenesis of pulmonary and cardiac complications

Statins have significant immunomodulatory properties in addition to reducing cholesterol. Pulmonary complications such as ARDS is an inflammatory condition driven by inflammatory

cells such as neutrophils[23] and macrophages[24]. There is an associated release of inflammatory mediators, cytokines, reactive oxygen species (ROS) and nitric oxide derived reactive nitrogen species[25]. This uncontrolled local inflammatory response causes alveolar epithelial and capillary endothelial barrier damage[26, 27] central to the development of lung injury[25]. The small GTPases Rho and Rac are involved in signal transduction linking extracellular stimuli to epithelial and endothelial barrier function [28]. Similarly systemic inflammatory response due to pulmonary or systemic insult is associated with endothelial dysfunction[29]. Endothelial dysfunction is also central to myocardial ischaemia secondary to plaque instability. Published evidence supports the role of inflammation and endothelial dysfunction in the atherosclerotic process[30,31] central to the development of atherosclerotic plaque instability[32].

Hydroxyl-methylglutaryl coenzyme A reductase inhibition with statins is a promising potential new therapeutic option since statins modulate a number of the underlying processes described in the development of pulmonary and cardiac complications. Statins have diverse anti-inflammatory properties[33] and 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[34].

A study examined how 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[35]. 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 lung injury in bronchoalveolar lavage fluid, including tumour necrosis factor (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[36].

Observational studies support a clinical trial of a statin to prevent pulmonary and cardiac complications

Acute respiratory distress syndrome is the most common complication of severe sepsis [37]. In patients with sepsis most [38-41] observational studies suggest that statins are associated with better outcomes, as measured by morbidity and mortality. Similarly, most [42-44] observational studies have suggested a beneficial effect of statins in patients with pneumonia, supporting a potential role for statins in modulating pulmonary inflammation. A recent meta-analysis, which included more than 2000 patients undergoing surgery, concluded that pre-operative statin use was associated with a significant reduction in post-operative myocardial infarction, AF and length of hospital stay[45].

The Irish Critical Care Trials Group (ICCTG) have undertaken a prospective observational study in patients with ARDS, 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)[46]. Similarly, in a recent retrospective study, statin usage in patients with ARDS was associated with increased VFDs and reduced mortality, although again this was not significant[47]. These observational studies were not powered to examine the effect of statins on mortality. In a more recent observational study in patients with sepsis associated ARDS, statin therapy was associated with a significant reduction in lower admission Sequential Organ Failure Assessment score (SOFA) score, higher vasopressor free days and reduced mortality in patients with severe ARDS. Simvastatin was the most frequently used statin in the group of subjects studied. There was also a significant reduction in CRP and procalcitonin levels at admission in patients on statins when compared to non-statin users[48].

Rationale for statin as a preventative therapy

Sepsis is the predominant cause for the development of ARDS. The benefit of statins in reducing adverse outcomes including mortality has been demonstrated in observational studies. In a recent met-analysis which included 26 studies with a combined study population of 337,648 patients, prior statin use was associated with both an unadjusted and adjusted risk of mortality[49]. In a different cohort of patients with abdominal aortic aneurysm (AAA), a population based case-control study has shown that statin use was associated with a reduced risk of ruptured AAA and lower case fatality following the rupture suggesting benefit from long term use of statin[50]. While the mechanism of action of statin is unclear, it is plausible that its pleiotropic anti-inflammatory effects have a role to play. These observational studies suggest that long term statin use may be associated with the prevention of adverse outcomes.

The outcomes reported in the observational studies are supported by data from randomised controlled trials which studied a shorter duration of acute use of statin in preventing the development of various clinical conditions. In a two centre open labelled randomised study, statin use was associated with a higher probability of being free of ventilator associated pneumonia[51] and the probability of survival was higher in the patients with increased severity index as measured by Acute Physiology and Chronic Health Evaluation II (APACHE II) score. A reduced progression to severe sepsis was also demonstrated in the ASEPSIS trial which was a single centre randomised placebo controlled study where patients assigned to atorvastatin had a significantly reduced incidence of conversion to severe sepsis[52]. These results are supported by another multi-centre, prospective, randomized, double blind, placebo-controlled trial stratified by site and prior statin use. This study demonstrated that patients who were randomised to the continued statin use arm of the study had reduced mortality and that prior statin use was associated with lower inflammatory cytokine levels at baseline[53].
Randomised controlled trials in non-cardiac surgery patients have shown a significant reduction in cardiovascular mortality and cardiac events post-operatively[54]. A similar improvement in pulmonary complications was shown in patients undergoing pulmonary resection who were randomised to receive atorvastatin 40mg or placebo prior to surgery[55].

These studies demonstrate the benefits of statins in preventing pulmonary and cardiac complications post-surgery and the biological rationale for these effects.

Proof of concept that simvastatin prevents pulmonary and systemic cellular dysfunction and reduces inflammation in patients undergoing one lung ventilation

We have completed a single centre, randomised, double-blind, placebo-controlled phase II study of simvastatin (80mg for up to 11 days) in 31 patients undergoing oesophagectomy. In this proof of concept study, pre-treatment with simvastatin in oesophagectomy decreased biomarkers of inflammation as well as pulmonary epithelial and systemic endothelial injury. Simvastatin resulted in a significant decrease in plasma MCP-1 on day 3 and reduced Exhaled Breath Condensate (EBC) acidification. There was a reduction in plasma RAGE on day 7 and urine ACR on day 3 post surgery. ARDS developed in 4 patients in the placebo group and no patients in the simvastatin group although this difference was not statistically significant but this study was not powered to study clinical outcomes. Importantly simvastatin 80mg was well tolerated with no increase in AEs[56].

The intervention has acceptable side effects

Statins have been proven to be a well-tolerated class of drugs. Simvastatin 80mg is within the licensed therapeutic range for the treatment of hypercholesterolaemia. Although in 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 simvastatin 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[57]. 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, 6031 patients with a history of myocardial infarction were randomised to receive simvastatin 80mg, myopathy occurred in 0.9% and rhabdomyolysis in 0.18% receiving simvastatin 80mg. Participants were seen at follow-up, 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 the Prevention-HARP 2 study is only 17 days with safety monitoring (CK and liver transaminases) at baseline, day of surgery, day 3 and day 7 post surgery.

In patients undergoing surgery, perioperative use of statins has been shown to be beneficial. A recent meta-analysis which included 29 randomised controlled trials has shown that perioperative statin use in patients undergoing high risk cardiac procedures is associated with a reduced myocardial infarction rate and also a trend in a reduction in one year mortality[58]. A similar beneficial effect on mortality, stroke, atrial fibrillation, and length of stay in hospital has been confirmed in a meta-analysis from 32 studies of 36,053 statin pre-treated coronary artery bypass graft surgery patients compared with control subjects[59].

While there are no trials studying the safety of statins in patients undergoing oesophagectomy, the data from our proof of concept study reassuringly found that simvastatin 80mg was well tolerated and not associated with increased 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, liver transaminases (alanine transaminase (ALT) and aspartate aminotransferase (AST) between the groups. There were no differences in AEs or SAEs between the groups. No drug-related SAEs occurred during the study. Furthermore, the incidence of clinical adverse outcomes such as ARDS, infections, arrhythmias were lesser in the simvastatin treated group when compared to the placebo group but this study was not powered to detect clinical outcomes.

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.

5.3 Rational for the Intervention

5.3.1 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. Simvastatin 80mg has been studied in a pre-treatment model of pulmonary inflammation using inhaled LPS[35 and also in the proof of concept study for efficacy in oesophagectomy patients[56] and will be investigated in this study. It is important to emphasise the maximum treatment period with simvastatin 80mg in the Prevention-HARP 2 study is only 17 days with safety monitoring at baseline, day of surgery, day 3 and day 7 post surgery.

5.3.2 Rationale for simvastatin 11-day duration of treatment

The decision to investigate treatment for 4 days pre-surgery up to 7 days post-surgery is based on: 1) data from our proof of concept study demonstrating on-going clinical improvement to day 11; 2) amelioration of inflammatory response to inhaled endotoxin challenge in healthy volunteers pre-treated for 4 days with simvastatin[35]; and 3) most post-operative complications occur within 7 days post-operatively[17].

5.3.3 Rationale for simvastatin 80mg dosage

Although there is a large amount of data suggesting statins may be beneficial in animal models of ARDS, 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[60].

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[61].

Simvastatin 80mg is the only dose with proof of concept data and is well tolerated in oesophagectomy patients 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 a maximum of 17 days and these patients will be closely monitored.

Lack of published randomised controlled trials of statins in preventing post one lung ventilation pulmonary and cardiac complications

There is a paucity of pharmacotherapy for ARDS and there is an urgent need to reduce postoperative cardiac and respiratory complications. ARDS after one lung ventilation is similar in pathophysiology to ARDS from other causes with no definitive treatment to prevent or treat this clinical condition with a high morbidity and mortality. A recent Cochrane review (2004) highlighted this and concluded "Effective pharmacotherapy in ARDS is extremely limited, with insufficient evidence to support any specific intervention" and stressed the need for further clinical trials in this area. There are no published studies addressing the prevention of both pulmonary and cardiac complications after one lung ventilation using statins.

The intervention is simple and inexpensive

Simvastatin is an inexpensive treatment readily available from generic drug manufacturers and costs less than £5 for 11 days treatment. By comparison the cost per ICU bed-day exceeds £1200.

5.4 Rationale for Comparator

There is no proven pharmacotherapy to prevent cardiac and respiratory complications after oesophagectomy, lobectomy or pneumonectomy. A placebo arm will be used as a comparator to study the benefits of the active drug, simvastatin, in the absence of an established standard treatment to prevent these complications. A placebo arm is also essential to ensure adequate blinding of participants and the research team involved in this study.

6 STUDY AIM AND OBJECTIVES

6.1 Research Hypothesis

We hypothesise that simvastatin 80mg when compared to placebo will reduce cardiac and pulmonary complications in patients undergoing elective oesophagectomy, lobectomy or pneumonectomy.

6.2 Study Aim

The aim of this study is to test the hypothesis that treatment with enteral simvastatin 80mg once daily for four days pre-surgery and up to 7 days post-surgery will prevent cardiac and respiratory complications in patients undergoing elective oesophagectomy, lobectomy or pneumonectomy.

6.3 Study Objectives

The study has two distinct objectives:

6.3.1 Primary objective

1. To conduct a prospective randomised, double-blind, placebo-controlled phase II multi-centre trial of simvastatin for the prevention of cardiac and pulmonary complications in patients undergoing elective oesophagectomy, lobectomy or pneumonectomy.

6.3.2 Secondary objectives

2. To study the biological mechanisms of simvastatin treatment on:

    a. Systemic markers of inflammation;
    b. Systemic cell-specific indices of activation and injury to the alveolar epithelium and endothelium;
    c. Lung extracellular matrix degradation; (2d) systemic endothelial injury and effect on non-pulmonary organ dysfunction.

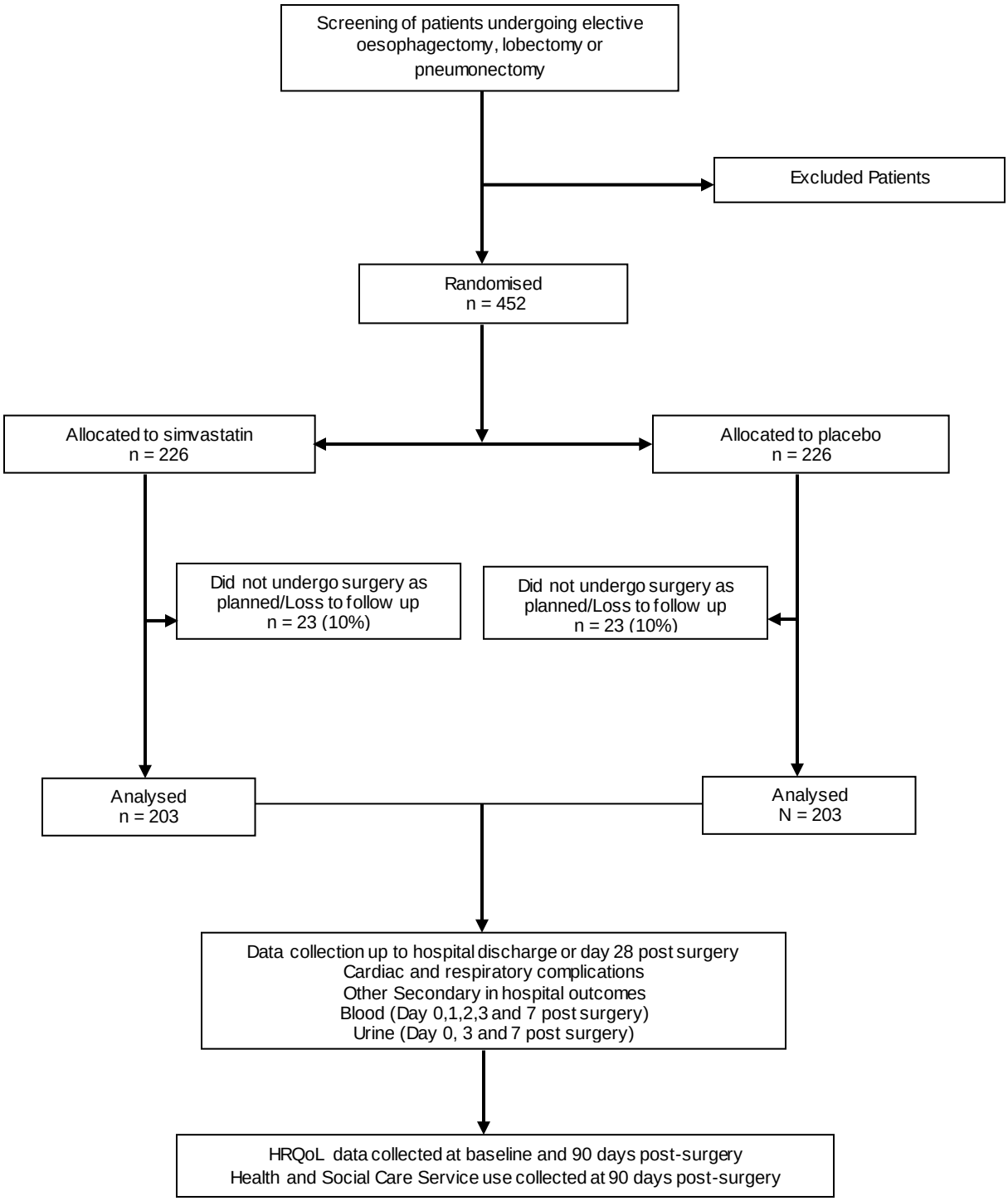
7 STUDY DESIGN

7.1 Study Design

Prospective, randomised, double-blind, placebo-controlled phase II multi-centre trial of simvastatin in patients undergoing elective oesophagectomy, lobectomy or pneumonectomy.

7.2 Study Schematic Diagram

Figure: 1 Study Schematic Diagram



7.3 Study Timeline

Table: 1 Study timeline Gantt Chart

PROPOSED TRIAL MILESTONES *Start date TBC* *Recruitment complete month 51*

Year	***1***				***2***				***3***				***4***				***5***			
Quarter	***1***	***2***	***3***	***4***	***1***	***2***	***3***	***4***	***1***	***2***	***3***	***4***	***1***	***2***	***3***	***4***	***1***	***2***	***3***	***4***
Project - months	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60
Trial Set-up	X	X																		
Site Training	X	X																		
Main Study			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Patient Recruitment			X	X	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	X	X	X		
HRQoL Follow-up				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Resource use				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Survival Status				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Management Meetings	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DMEC	X				X		X		X		X		X		X		X		X	
TSC	X						X				X				X				X	
Data Analysis																			X	
Trial Publication					X															X
Trial Close Down																				X
Dissemination																				X

8.0 METHODS: PARTICIPANTS, INTERVENTIONS, AND OUTCOMES

8.1 Study Setting

This will be a multicentre trial with patients recruited from secondary care centres throughout the UK. A list of centres will be maintained in the Trial Master File.

8.2 Eligibility Criteria

Patients will be recruited to the study when they fulfil the following inclusion and exclusion criteria and are deemed by a medically qualified member of the research team to be eligible to participate in the study.

8.2.1 Inclusion criteria:

1. Adult patient's ≥18 years of age undergoing one lung ventilation for elective oesophagectomy, lobectomy or pneumonectomy will be eligible for inclusion in the study.
2. Female subjects must be surgically sterile, or be postmenopausal, or must agree to use effective contraception during the period of the trial and for at least 30 days after completion of treatment. A pregnancy test measured by urine HCG in females with child bearing potential will be performed at pre-operative assessment clinic

8.2.2 Exclusion criteria:

1. Age < 18 years
2. Known active liver disease (Child's Pugh score > 11), or abnormal liver function tests: transaminases (AST or ALT) ULN > 3 times upper limit normal range (ULN) of local laboratory range
3. Renal impairment (calculated creatinine clearance less than 30mL/minute)
4. Inability to take medication enterally pre-operatively
5. Subject reported lactose intolerance
6. Participation in other intervention trials within 30 days
7. Current treatment with statins
8. Known hypersensitivity to the study medication
9. Previous adverse reaction to statins
10. Concomitant use of fibrates or other lipid-lowering therapy
11. Concomitant use of itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprivir, telaprevir, nefazodone, cobicistat, cyclosporine, danazol, amiodarone, amlodipine, verapamil or diltiazem, fusidic acid, and niacin.
12. Dated informed consent indicating that they understand all the pertinent aspects of the trial prior to enrolment
13. Currently pregnant or lactating

8.2.3 Co-enrolment guidelines

Patients enrolled in other investigational drug studies are not potential candidates for this study if within 30 days of the first dose of Prevention HARP 2 study drug. Patients enrolled in other interventional studies or observational studies are potential candidates for this study.

8.2.4 Trial centre requirements

Units performing elective oesophagectomy, lobectomy or pneumonectomy 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. Prior experience in recruiting for multicentre trials and PI with experience in recruiting for multicentre trials
5. Documented willingness to comply with the protocol, Standard Operating Procedures (SOPs), the principles of Good Clinical Practice (GCP) and regulatory requirements

8.2.5 Research Team Requirements

Staff must demonstrate and document a willingness to comply with the protocol, standard operating procedures, trial specific procedures, the principles of GCP and regulatory requirements and be prepared to participate in locally-delivered trial-specific training.

8.3 Interventions

8.3.1 Intervention description

Patients will be randomised to receive once daily simvastatin 80mg (as two 40mg tablets) or 2 matched placebo tablets administered enterally. Patients will self-administer the medication orally or through a feeding tube for 4 days pre-operatively and postoperatively the study drug will be administered by the ward nurse via a feeding tube for up to 7 days. Patients will record self-administration of the drug in a patient diary pre-surgery. In the event of postponement of the date of surgery, the patient will stop the study drug and start it again once a date for surgery has been confirmed again. The total duration of the course will be 11 days if there is no postponement of surgery and up to 17 days if surgery is postponed.

In the event of a postponement, the study drug can be stopped and restarted for 2 such episodes of postponements. The maximum duration of the course will be 17 days if postponed twice. This will allow 3 additional days per postponement of surgery. Simvastatin administered post-surgery via enteral tube is well tolerated and absorbed adequately as demonstrated in our proof of concept study.

8.3.2 Intervention discontinuation

Study drug will be discontinued if any one of the following conditions is met, prior to the maximum treatment period (up to 17 days from start of study drug):

1. Study drug related AE
    a) CK > 10 times the upper limit of normal (ULN) of local laboratory range
    b) ALT/AST > 5 times the ULN of local laboratory range
2. Development of a clinical condition requiring immediate treatment with a statin
3. Discontinuation of active medical treatment
4. Patient's request for withdrawal from the study

5. Decision by the attending clinician that the study drug should be discontinued on safety grounds
6. Discharge from hospital
7. Change of type of surgery (Patients will be followed up for AE/SAE as per protocol)
8. Death

8.3.3 Intervention adherence

Adherence to the study drug will be monitored by recording the number of tablets returned at the end of the treatment period which will be used to calculate the number of doses administered. The patients will also maintain a diary record of self-administration prior to admission for their surgery. Patients will need to have taken at least one dose of the study drug prior to the surgery for inclusion into the trial.

8.3.4 Concomitant care

Usual standard of care including all rescue interventions are allowed. Interventions with anti-inflammatory effects such as Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids should only be used if deemed necessary and are not contraindicated. Use of NSAIDs and corticosteroids will be captured in the Electronic Data Capture (EDC).

8.4 Outcome Measures

8.4.1 Primary Outcome Measure

The primary outcome measure is a composite endpoint of the incidence of ARDS defined according to the Berlin definition[62] (See Appendix I), post-operative pulmonary complications (PPC) as defined by Melbourne group scale[63] (See Appendix II) and myocardial infarction as defined by ischaemic chest pain (See Appendix III), ECG changes and a raise in plasma troponin and also by myocardial ischaemia post non-cardiac surgery (MINS) criteria[64] (See Appendix III) during the first seven days post operatively or hospital discharge if earlier. These end points were chosen based on their effect on short term and long term outcomes and a biological rationale for statin in modulating these endpoints.

8.4.2 Secondary Outcome Measures

Secondary outcomes include clinical outcomes, safety and health economic outcomes (HRQoL and costs).

8.4.2.1 Clinical Outcomes

1. Mortality at day 28 and day 90
2. Ventilator free days (VFDs)[65] and are defined as the number of days in the first 28 days following surgery that a patient is free from ventilator assistance, for greater than 48 hrs.
3. ARDS, PPC and MI within 28 days of surgery or hospital discharge if earlier
4. Atrial fibrillation within 28 days of surgery or hospital discharge if earlier
5. Venous thromboembolism[66] within 28 days of surgery or hospital discharge if earlier
6. Incidence and nature of any surgical complications will be recorded
7. ARDS within 7 days of surgery of hospital discharge if earlier.

8. PPC within 7 days of surgery or hospital discharge if earlier.
9. MI within 7 days of surgery or hospital discharge if earlier.
10. MINS within 7 days of surgery or hospital discharge if earlier

8.4.2.2 Safety

1. CK >10 times the upper limit of normal (day 0, day 3 and day 7 post-surgery) of local laboratory range
2. ALT/AST >5 times the upper limit of normal (day 0, day 3 and day 7 post-surgery) of local laboratory range
3. Acute kidney injury defined according to KDIGO guidelines (using change from baseline serum creatinine) within seven days of surgery
4. SAEs, AEs and occurrence of SUSARs as defined in section 11.10.1

8.4.2.3 Health Economic Outcomes

1. Health related quality of life (HRQoL):
    - EQ-5D-5L at baseline and at 90 days' post-surgery.

2. Health and Social Care 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 90 days' post-surgery

8.4.2.4 Exploratory analysis

Biological mechanisms

1. 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) and RAGE ligands
2. Neutrophil activation biomarkers which may include but are not limited to measurement of plasma MPO and neutrophil elastase
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 (PIIINP)
6. Peripheral blood NF-κB activation
7. Plasma cotinine level

8.5 Participant Timeline

Table: 2 Schedule of enrolment, interventions and assessments

Time	Pre-screening	Baseline screening	Pre-admission	Day of surgery	Post-op Day 1-7	Post-op Day 8 - 28	90 days post-surgery
Eligibility Screen[1]	X						
Patient Invitation Letter	X						
Eligibility Assessment[2]		X					
Informed consent		X					
Demographics[3]		X					
Medical history[4]		X					
Pre-surgery Chemotherapy [5]		X					
Pregnancy test[6]		X					
Randomisation		X					
Study drug dispensing		X					
Patient diary issue		X					
Issue emergency contact card		X					
Telephone call to participant [13]			X				
Study drug administration				X	X		
Primary outcome[£]				X	X		
Secondary outcomes[£]				X	X	X	
Simvastatin level [7]				X	Day 7		
Dexamethasone				X			
PaO2:FiO2 ratio[8]					If available		
Blood sampling (safety)[9]		X		X	Day 3 and 7		

Blood and urine sampling[10] (mechanisms)		X		X	Day 1,2, 3 and 7		
Surgery type				X			
Intra-operative fluid balance				X			
Duration of OLV[11]				X			
Duration of ventilation				X			
Intra-operative tidal volume				X			
AE/SAE/SUSAR			X	X	X	X	
Survival status status[12]				X	X	X	X
HRQoL assessment (EQ-5D-5L)		X					X
Level of care (Resource use)				X	X	X	
Health and social care service use							X

[1] Eligibility screen – (Age, prior statin use, use of other contraindicated medications)
[2] Eligibility assessment – 5 ml blood for AST, ALT, CrCl if not available
[3] Demographics – Age, Gender, Height, Weight, BP, FEV1/FVC ratio
[4] Medical history – including but not limited to: Angina, MI, COPD, Diabetes, Concomitant Medications, Smoking Status
[5] Pre-surgery Chemotherapy – Yes/No
[6] Pregnancy test measured by urine HCG in females with child bearing potential
[7] Simvastatin – Day of surgery and D7 blood sample
[8] PaO2:FiO2 ratio Day 1 to Day 7(if available)
[9] Blood sampling (safety) – ALT, AST, serum creatinine and CK. In the event that safety bloods samples are due to be collected on bank holidays or weekends, these samples may be taken at the next working day and the deviation noted.
[10] Blood sampling (mechanism) – See Trial manual for sample handling. Day 1, 2 and 3 also include troponin and hence are essential
[11] OLV – One lung ventilation.
[12] Will be checked at day 28 or prior to hospital discharge and at day 90 post surgery
[13] Research nurse to instruct participant to commence taking study drug, complete their study diary and to check that the study drug is within expiry for the entire duration of its course
[£]Primary and secondary outcomes are defined in section 10.5

8.6 Blood and urine Sampling (Mechanisms)

Blood and urine will be taken at baseline screening visit prior to study drug administration, on the day of surgery pre-induction, day 1, 2, 3 and 7 post-surgery from all patients. In the event that research samples are due to be collected on bank holidays or weekends, or are not able to be taken due to non-availability of research staff, these samples may be taken up to 2 days after the due date, (with the exception of baseline and the day of surgery which must be taken as per schedule). Heparinised blood samples (20 mL) and urine samples (10 mL) will be collected at each time point. The blood samples will be processed according to study specific sample handling guidelines. Plasma from heparinised blood along with aliquots of urine will be stored at - 20 °C initially at the local site until transfer to the Respiratory Research Laboratory at the Queen's University of Belfast (QUB) where they will be stored at in a monitored -80 freezer in the cTIMP lab in the Medical Biology Centre of QUB until analysis. Blood and urine will be stored beyond study completion for additional biomarker studies. Samples will be labelled with the patient's unique trial identifier.

If there is a clinical reason that samples cannot be collected, this will not be recorded as a protocol violation but at least one blood sample will be needed between day 1 and day 3 post surgery. The reason will be documented.

8.7 Sample Size

There is limited data in the literature regarding the incidence of cardiac and pulmonary complications after oesophagectomy, lobectomy or pneumonectomy. The incidence of these complications is varied ranging from 13 – 43% in the literature[63, 67] [17-19, 68, 69]. In the NCEPOD report in 1997, 27% of oesophagectomy patients developed respiratory failure, most were due to the development of ARDS. In a more recent 2013 national audit of patients undergoing oesophagectomy in England and Wales, cardiac and respiratory complications accounted for more than 50% of the complications. The incidence of ARDS in our proof of concept study was 25% in the placebo group. The incidence of myocardial infarction ranges from 5% - 8% based on the MINS criteria [10, 64].

There are no prospective randomised controlled trials in surgeries utilising one lung ventilation technique in patients to predict the size of the treatment effect on preventing cardiac and respiratory complications post-surgery. In a cohort study there was a 11% absolute difference in the development of ARDS between patients treated with ketoconazole compared to historical controls (5% vs 16%)[70]. In a case control study at two hospitals in Canada, the incidence of ARDS fell from 35% to 5% (30% absolute reduction) in response to prophylactic administration of ketoconazole prior to surgery[71].

There are no studies of statins in preventing myocardial infarction in patients undergoing surgeries utilising one lung ventilation technique. In patients undergoing vascular surgery, fluvastatin pre-treatment reduced the risk of myocardial infarction from 20% to 10%[54]. In a randomised placebo controlled trial simvastatin pre-treatment was associated with a 37% absolute reduction in troponin release[72].To inform on the likely loss to follow-up, previous randomised controlled trials in oesophagectomy patients have experienced a 1- 2% loss to follow up rate over 7 days[73, 74]. The recently completed UK ITU pulmonary artery catheter study had a 2.4% loss to follow up[75].

The preliminary sample size of 203 is based on a two group Chi-square test with 50% relative reduction in incidence of the composite endpoint from a predicted rate of 25% in the control group with 90% power of detecting this difference at p=0.05. The inclusion of a 10% drop out rate gives an overall sample size of 226 per arm or 452 in total. Our proof of concept study indicates that 70% of patients would fulfil the criteria for enrolment. A recent trial of statins in patients with ARDS, the exclusion rate due to prior statin use was 30% with a further 10% refusing assent/consent[76].

A recent trial (Prevention BALTI) successfully recruited patients at a rate of 16/month from 12 UK sites with an 80% recruitment rate[3]. The planned recruitment site of 12 with a conservative recruitment rate of 50% which includes a 10% failure to progress to surgery will enable completion of recruitment in 45 months at the rate of 10/month.

8.8 Recruitment

8.8.1 Recruitment strategy

Based on the proof of concept study and the HARP trial, we expect 30% of patients to be excluded due to prior statin use. We anticipate a further 10% refusal to consent for this research proposal. A planned recruitment of 50% of patients undergoing elective oesophagectomy, lobectomy and pneumonectomy will allow a further 10% loss of recruitment due to other reasons. The sample size calculation has also built in a 10% drop out due to surgical cancellations/delay. A recent multicentre trial, Prevention BALTI, identified potential 20 oesophagectomies/month across 12 UK sites". We anticipate a 10/month recruitment rate across approximately 15 sites. For a sample size of 452, we will need 45 months to recruit at the rate of approximately 1 patient/month/site.

To maximise recruitment, the patients will be identified early in multidisciplinary meetings. Competing studies have been identified and screening will be conducted in parallel for the identified competing study.

The UK sites identified will be based on the volume of surgery, presence of infrastructure to support research and the experience of PI in recruiting for multi-centre trials. We will also identify further sites to which the study can be rolled out in the event of less than anticipated recruitment rate.

No financial incentive has been planned for trial investigators or participants.

8.8.2 Screening procedure

Potential participants will be identified at the local cancer multi-disciplinary meeting (MDM) or from pre-op assessment waiting lists. Patients may be screened by the research team to assess whether they meet the inclusion criteria and none of the exclusion criteria. The patient will then be provided with a copy of the patient information sheet >24hours prior to their pre-assessment clinic or approached directly at the pre-assessment clinic, if referred from a peripheral hospital. This will enable them to have the opportunity to discuss their participation with others. If interested, the study will be discussed in detail with the patient and they will be invited to take part. The patient will also be offered the opportunity to attend for a further visit to the clinic if necessary to discuss their participation. If agreeable to taking part in the study, written informed consent will be obtained from the patient by a trained member of the research team. The PI or sub-investigator will confirm that the patient fulfils the inclusion and exclusion

criteria for the study. The subjects' eligibility will be confirmed and documented by a medically qualified doctor on the delegation log of the trial.

The PI will retain a 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.

8.8.3 Informed consent procedure

When the patient attends the outpatient pre-operative assessment clinic they will be asked to consent to participate in the trial and to sign the consent form, which will then be countersigned by a trained member of the research team. A copy of the signed consent form will be placed in the patient's medical records whilst the original will be retained by the PI in the Investigator Site File (ISF) and the patient will also be given a copy. If the patient refuses consent, the patient will not be entered into the trial but their details will be entered in the screening log.

8.8.4 Withdrawal of consent

Patients may withdraw or be withdrawn 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 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 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 wishes to withdraw from the trial after completion of trial treatment, permission to access medical records for trial data will be sought.

9 STUDY DRUG

9.1 Study Drug Description

Simvastatin is HMG-CoA reductase (3 hydroxy – 3 methylglutaryl CoA reductase) inhibitor which also has anti-inflammatory activity. The study drug will be in the form of tablet which will be taken orally or through a feeding tube for 4 days before surgery and for up to 7 days after surgery. After surgery, the study drug will be administered via a feeding tube which is placed routinely after surgery. The study drug will be dispersed in 10 - 20 ml of water when administered via the feeding tube.

9.2 Study Drug Supply

Patient drug packs will be prepared by Victoria Pharmaceuticals, The Plenum Building, Royal Hospitals, Grosvenor Road, Belfast, BT12 6BA, UK. Simvastatin 40mg or matching placebo tablets will be packaged in a white opaque high density polyethylene (HDPE) plastic container which will be sealed with a tamper-evident seal and labelled in compliance with applicable regulatory requirements. Each container will contain 40 tablets of study drug for the treatment of one patient for 20 days (which includes 9 days overage to allow for surgical delays and also drug wastage by accident). All trial drugs will be packaged identically and identified only by a unique medication pack identification number in accordance with the study randomisation sequence.

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.

When a patient is recruited, the research team will contact the randomisation service to obtain the unique medication pack identification number 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 pack number assigned to the patient. The hospital pharmacy will dispense the allocated drug pack. The drug pack will contain all study drugs necessary to give a complete course of trial treatment to one patient.

9.3 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. Records must be available to the study monitors on request. Unallocated, unused and used study drug will be destroyed at site with permission from the CTU and in accordance with site pharmacy procedure for destruction of IMP and hospital waste management policies. A record of the destruction will be maintained.

9.4 Study Drug Storage

The study drug should be stored as per manufacturer's recommendation.

9.5 Study Drug Administration

A member of the research team will contact the patient by telephone, or with them face to face, 4 days prior to their planned surgery date to remind them to commence taking the study drug and to complete their patient dairy.

The patient will be instructed to start taking the study drug four days prior to the surgery.

In the event of delay or postponement of the surgery the study medication will be stopped and then restarted 4 days prior to the new date of surgery. Prior to surgery, including the day of surgery, the study medication can be self-administered by the patient or can be prescribed and administered by the clinical care team. Pre-operative study drug administration will follow usual clinical care advice. Post-operatively the study drug will be administered via a feeding tube, which is placed routinely after surgery until oral intake is recommenced. The study drug will be dispersed in 10 - 20 ml of water when administered via the feeding tube. Post-operatively the study drug will be administered by the ward nursing team who will not be involved in any of the study specific assessments.

9.6 Study Drug Termination

Study drug will be discontinued if any one of the following conditions is met, prior to the maximum treatment period (11 days from start of study drug):

1. Study drug related AE
    a) CK > 10 times the upper limit of normal (ULN) of local laboratory range
    b) ALT/AST > 5 times the normal ULN of local laboratory range
2. Development of a clinical condition requiring immediate treatment with a statin or other drugs which interact with statins
3. Discontinuation of active medical treatment
4. Patient's request for withdrawal from the study
5. Decision by the attending clinician that the study drug should be discontinued on safety grounds
6. Discharge from hospital
7. Change of type of surgery
8. Death

9.7 Clinical Management of Patients in the Trial

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

Standardised intra-operative management – Anaesthetists will be encouraged to use an epidural catheter for pain management, a protective ventilator strategy with tidal volumes of 6 - 8ml/ Kg ideal body weight, PEEP of 5 cm H_2O and a plateau pressure < 28cm H_2O, conservative use of fluids and avoid non-steroidal and corticosteroid use. Details of the intra-operative management strategy used will be recorded by research staff at each site.

9.8 Need for statin treatment in addition to the study drug

The exclusion criteria prevent patients 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 Case Report Form (CRF). Otherwise patients will not be commenced on a statin for the duration of the clinical trial.

9.9 Sequence Generation

Eligible participants will be allocated to intervention or placebo using an automated randomisation system. After obtaining informed consent, patients will be randomised on a 1:1 allocation ratio pre-operatively stratified by centre. The randomisation sequence will be saved in a restricted section of the TMF which only be able to be accessed by statisticians and not those who enrol or assign interventions.

9.9.1 Allocation Concealment Mechanism

The randomisation sequence will be concealed using a number of measures including:

i) Using an automated randomisation system
ii) Restricting access to the randomisation sequence

9.9.2 Allocation Implementation

When the research team at each study site identifies a patient suitable for enrolment, they will obtain informed consent for participation in the trial. 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.

Treatment allocation will be assigned using an automated randomisation process that each site research team will complete. Patients will be randomised to receive once daily simvastatin 80mg (as two 40mg tablets) or 2 matching placebo tablets self-administered enterally via a feeding tube or orally for 3 days prior to surgery, on the day of surgery and for up to 7 days post-surgery by the ward nurse. In the event of surgical postponement, the study drug will be stopped and restarted once a new date for surgery has been confirmed. Allowing for 2 such postponements, which will add a maximum of 6 added days of study drug administration, the total maximal duration of course of study drug will be 17 days. Treatment allocation will be blinded.

9.9.3 Blinding

This is a double blind placebo controlled trial, patients, clinicians and the study team will be blinded to each patient's treatment allocation. All trial drugs, whether simvastatin or placebo, will be packaged identically and identified only by a unique medication pack identifier.

9.9.3.1 Emergency unblinding

Emergency unblinding may be requested by a PI or designated investigator on safety grounds, or if the treatment decision for a patient could be influenced by the knowledge of what the patient is taking as part of the trial. If the PI or designated Investigator decides that there is justification to unblind a patient, emergency unblinding will be performed via the randomisation system. In the event of failure of the online system, back up manual unblinding can be performed by the clinical trials pharmacist between 9 am – 5 pm or the on call pharmacist out of hours in the Royal Victoria Hospital, Belfast. If time permits, the PI should attempt to contact the CI prior to unblinding. In the event unblinding occurs, the patient may discontinue the study drug but will remain on the trial unless they decide to withdraw. Where unblinding has occurred this should be fully documented by the site and the CTU informed.

10 METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

10.1 Data Quality

The CI and/or NICTU will provide training to site staff on trial processes and procedures including EDC completion and data collection. Within the NICTU the clinical data management process is governed by SOPs which help ensure standardisation and adherence to International Conference of Harmonisation Good Clinical Practice (ICH-GCP) guidelines and regulatory requirements.

On-site monitoring visits during the trial will check the accuracy of EDC entries against source documents alongside adherence to the protocol, trial specific procedures and GCP. This monitoring will be carried out as per the trial specific monitoring plan.

Data validation will be implemented and discrepancy reports will be generated following data entry to identify data that may be out of range, inconsistent or protocol deviations based on data validation checks programmed into the clinical trial database.

A Data Monitoring & Ethics Committee (DMEC) will be convened for the study to carry out reviews of the study data at intervals during the study.

10.2 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 the protocol, EDC database, completion of the CRF and trial procedures including any applicable SOPs.

10.3 Pre-Screening

- Participant identification
  - From Multidisciplinary meetings/ waiting lists
  - Check eligibility from medical notes – Age < 18 years
  - Prior statin use and use of other contraindicated medications as per exclusion criteria

- Send an invitation letter to potential participant along with a patient information sheet if “No” for all of the above.

10.4 Baseline Visit and Procedures

- Informed consent
- Eligibility review
- Blood for eligibility – Liver function and renal function test
- Baseline characteristics –
  - Age, gender, height, weight ,BP
  - Medical history – including but not limited to: Angina, MI, COPD, Diabetes, Smoking Status
  - Concomitant medication – Names of drugs
  - Pre-surgery Chemotherapy – Y/N, If yes – Number of cycles

    - Reason for surgery – Barrett's oesophagus, Squamous cell, adenocarcinoma, small cell carcinoma, other causes
    - Spirometry – FEV1/FVC ratio (if available)
    - Type of Planned Surgery: oesophagectomy, lobectomy, or pneumonectomy
    - Pregnancy test
- Randomisation and treatment allocation
- Drug script and dispensation only when eligibility is confirmed from the blood results at clinic. Randomisation and drug dispensation may occur after the participant's clinic visit. In such instances, arrangements will be made to deliver the drugs to the patient at home.
- Inform GP of patient's participation and provide them with a patient information sheet and list of prohibited medications and foodstuffs.
- EQ-5D-5L
- Serum and urine for storage – See trial manual
- Issue emergency contact card
- Issue subject dairy

Pre-admission

- Telephone check for AE, SUSARs, SAE
- Study drug compliance and drug expiry check
- Recording and reporting AE/SUSARs/SAE

10.5 Study Visits and Procedures

Day 0 (day of surgery)

- Study drug to be administered by clinical staff or self-administered by patient.
- Blood for liver function, renal function test and CK (5ml), to be performed prior to surgery
- Serum (20ml) and urine (10ml) for storage taken > 1 hour after study drug administration (Sample handling procedure in trial manual)
- Tidal volume, fluid balance, type of surgery (minimally invasive/ hybrid/open) duration of one lung ventilation, duration of ventilation, dexamethasone (Y/N)
- ARDS as per Berlin definition (Appendix I)
- PPC as per Melbourne Group Scale (Appendix II)
- MI as per symptoms, ECG and troponin (Appendix III)
- Atrial fibrillation (AF)
- Cardiac arrhythmias (excluding AF)
- Deep vein thrombosis/ pulmonary embolism (DVT/PE)
- Mechanical ventilation or non-invasive ventilation
- Incidence and nature of any surgical complications
- Survival status
- Resource use will be recorded daily until the patient is discharged
- Recording and reporting of AEs, SUSARs and SAEs

Day 1-7 post surgery or until hospital discharge if earlier

- ARDS as per Berlin definition (Appendix I)
- PPC as per Melbourne Group Scale (Appendix II)
- MI as per symptoms, ECG and troponin or MINS criteria (Appendix III)
- Atrial fibrillation (AF)

- Cardiac arrhythmias (excluding AF)
- DVT/PE
- Mechanical ventilation or non-invasive ventilation
- Incidence and nature of any surgical complications
- Survival status
- Serum for storage post-surgery (Day 1, 2, 3 and 7) (Sample handling in trial manual)
- Urine for storage (Day 3 and 7) (Sample handling in trial manual)
- Blood for AST, ALT, SrCr and CK (Day 3 and 7)
- Resource use will be recorded daily until the patient is discharged
- PaO2/FiO2 ratio (if available)
- Recording and reporting of AEs and SAEs

Day 8 – 28 or until hospital discharge if earlier

- ARDS as per Berlin definition (Appendix I)
- PPC as per Melbourne Group Scale (Appendix II)
- MI as per symptoms, ECG and troponin or MINS criteria (Appendix III)
- Atrial fibrillation (AF)
- Cardiac arrhythmias (excluding AF)
- DVT/PE
- SrCr (where available)
- Mechanical ventilation or non-invasive ventilation
- Incidence and nature of any surgical complications
- Survival status
- Resource use will be recorded daily until the patient is discharged
- Recording and reporting of AEs, SUSARs, and SAEs

Day 90 follow up

- EQ-5D-5L to be completed and returned by the subject in a pre-paid envelope
- Resource use questionnaire to be returned by the subject in a pre-paid envelope
- Survival status

Recording of Data

All data for an individual patient will be collected by the PI or their delegated nominees and recorded in the EDC database for the study except 90 day follow up data. For the economic evaluation HRQoL will be measured by EQ-5D-5L at baseline and at 90 days' post-surgery. Resource use data will be collected via the questionnaire administered at 90 days' post-surgery.

Patient identification on the EDC database and questionnaires will be through their unique trial identifier allocated at the time of randomisation. Data will be collected and recorded in the EDC database and on the questionnaires by site research team from the time the patient is considered for entry into the trial through to their discharge from hospital. Data until 28 days' post-surgery will be entered into the EDC database and completed to agreed timelines.

10.6 Follow Up Visits and Procedures

All survivors will be followed up at 90 days after surgery. HRQoL will be measured using EQ-5D-5L administered at baseline and at 90 days' post-surgery. Health and social care resource use will be collected via a questionnaire at 90 days' post-surgery. Where the patient has been

discharged from hospital, questionnaires will be administered via post. Patient's consent will be obtained to get their permission to contact them should they not return their questionnaire. If questionnaires are not returned a maximum of two telephone contacts will be made to the study participant; the first call will check that the questionnaire has been received and the participant is happy to complete it. If necessary, a second copy of the questionnaire will be sent. In the event of non-return one further telephone contact will be made and the health economic data collected over the telephone where possible.

To minimise the risk of causing distress by contacting relatives of patients who have since deceased, the CTU will use a NHS central register and/or contact the patient's GP to ascertain the patient survival status prior to any contact being made.

10.7 End of Study Visit and Procedures

For the purposes of submitting the end of trial notification to the Sponsor, MHRA and REC the end of trial will be considered to be when database lock occurs for the final analysis.
The trial will be stopped prematurely if:

Mandated by the REC

Mandated by the MHRA

Mandated by the Sponsors (e.g. following recommendations from the DMEC)

Funding for the trial ceases

The RECs that originally gave a favourable opinion of the trial, the MHRA that issued the CTA will be notified in writing once the trial has been concluded or if terminated early.

10.8 Study Instruments

EQ-5D-5L

The EQ-5D-5L [77] is a generic preference-based measure of health which provides a description of health using five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) each with 5 levels of severity. Responses are converted to an overall utility score which will be used for the calculation of quality adjusted life years (QALYs). Respondents are also asked to place their health on a visual analogue scale (VAS) where 0 represents the worst imaginable health state and 100 the best imaginable health state. It is recommended by National Institute for Clinical Excellence (NICE) [78] for use in economic evaluations.

Resource Use Questionnaire

A resource use questionnaire has been developed specifically for the Prevention HARP-2 study. It will be administered at 90 days' post-surgery. It will capture the health services, such as community, social, hospital and care services, used by individuals during this time period following their surgery.

10.9 Participant Retention and Follow-up

Given the short duration of follow-up of 90-days, and the typically healthcare-compliant nature of cancer patients, difficulties with participant retention are not envisaged. This will be further

enhanced by the option to obtain outcome data by a combination of healthcare records review and telephone interview.

The participating site will provide an authorised member of the trial management team at the CTU with the name, address and contact details for the patient including mobile phone number and email. Trial subjects will be asked to let the CTU know if they move house at any time after hospital discharge. "

In the event of a request to withdraw from the study, the researcher will complete an off study form and determine which elements of the study are to be withdrawn please see section 8.7.4 for more information.

10.10 Data Management

Trial data (including logs and questionnaires) will be entered onto a web-based Clinical Trial Database (MACRO) by delegated personnel and processed electronically as per CTU SOPs and the study specific Data Management Plan (DMP).

Data queries will be 'raised' electronically (MACRO) by the CTU Data Manager where clarification from site staff is required for data validations or missing data. Site staff will 'respond' electronically to data queries ensuring that amendments where applicable are made to the Clinical Trial Database. The CTU Data Manager will review & 'close' (or re-raise) data queries as appropriate.

All essential documentation and trial records will be stored securely and access will be restricted to authorised personnel.

All study documentation and data will be archived as per regulatory requirements and those responsible for archiving will be noted on the sponsor delegation framework/mCTA.

10.11 Data Analysis

10.11.1 Analysis population

Primary analysis will be conducted on all outcome data obtained from all participants as randomised and regardless of protocol adherence, i.e. intention to treat analysis. Per-protocol analysis will also be conducted which will involve a comparison of treatment groups that includes only those patients who completed the treatment originally allocated. Patients that did not proceed with planned surgery or did not receive the pre-operative dose of drug will be excluded.

10.11.2 Statistical methods

10.11.2.1 Data Analysis

The primary outcome measure will be compared between treatment groups using a chi-square test. A secondary analysis will involve a logistic regression model, with the dependent variable as composite endpoint/no composite endpoint within 7 days and the independent variables as treatment, centre, type of surgery and age as a covariate. Other important covariates may be added to the model as specified in the Statistical Analysis Plan (SAP). We will also report each primary outcome component separately. An odds ratio measuring the treatment effect and its

95% confidence interval will be reported. Other categorical outcomes will be analysed using logistic regression models, with treatment group as an independent variable along with along with centre, type of surgery and age as a covariate. Other important covariates may be added to the model as specified in the SAP. The summary statistics will be based on proportions and the 95% confidence interval. Continuous outcomes will be analysed using linear regression models, with treatment group as an independent variable and terms for centre, type of surgery and age in the model. Other important predictors may be added to the model as specified in the SAP. Difference in treatment will be based on adjusted mean estimates and 95% confidence intervals. Time to event data will be analysed using a log-rank test. Any patients who have not experienced an event at the time point of interest or withdrawn will be censored. The proportion experiencing an event over time will be illustrated using a Kaplan-Meier curve for each of the treatment groups. The p-values and a hazard ratio with its 95% confidence interval from a Cox proportional hazards model will also be presented. The proportional hazard assumption across treatment arms will be checked graphically using a log-cumulative hazard plot.

Baseline characteristics, follow-up measurements and safety data will be described using appropriate descriptive summary measures depending on the scale of measurement and distribution.

A detailed SAP will be written by the trial statistician prior to the final analysis.

10.12 Health economics 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 90 days' follow-up (post-surgery). A health service perspective will be adopted for this analysis as recommended by the NICE [78] The outcome for the analysis will be the QALY and utilities will be measured using the EQ-5D-5L pre-surgery/baseline and at 90 days post-surgery. Resource utilisation will be collected at 90 days' post-surgery.

Resource utilisation will be quantified 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[79]. 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 given the duration of follow-up.

In all analyses, baseline characteristics will be controlled for, parameter uncertainty will be addressed using 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) assuming a societal willingness-to-pay of £20,000/QALY. A detailed health economic analysis plan will be finalised prior to commencing the analysis

10.13 Additional analyses

10.13.1 Interim analyses

An interim analysis will also be conducted to analyse efficacy and safety parameters. This will occur when approximately 50% of the planned number of patients to be randomised have completed day 28 or have been discharged from hospital, whichever is sooner. In relation to efficacy, a chi-square test will be applied with a p value <0.001 according to the Haybittle-Peto stopping rule. For safety, the acute kidney injury data will be presented alongside other safety data.

10.13.2 Subgroup Analysis

Subgroup analyses will use a statistical test for interaction and will be reported using 99% Confidence Interval. Four subgroup analyses are pre-specified, stratifying by chemotherapy prior to surgery (yes/no), type of surgery (oesophagectomy, lobectomy, pneumonectomy), surgical technique (minimally invasive/hybrid/open) and duration of one lung ventilation (≤120 mins and > 120mins [16]). We shall also investigate subgroups based on smoking status. Further detail will be given in the SAP.

10.14 Missing data

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

11 METHODS: MONITORING

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.

11.1 Data Monitoring and Ethics Committee (DMEC)

Specific Role:

Review of the DMEC report including updated information on recruitment, adherence to protocol treatment, data quality, and follow up and main trial outcomes and safety data. The specific roles of the DMEC should be defined by the members and may include to:

- Monitor recruitment figures and losses to follow up
- Monitor evidence for treatment differences in the main efficacy outcome measures
- Monitor evidence for treatment harm (e.g. toxicity, SAEs and deaths)
- Monitor compliance with the protocol by participants and investigators
- Monitor planned sample size assumptions
- Assess data quality, including completeness (and by so doing encourage collection of high quality data)
- Assess the impact and relevance of external evidence
- Suggest additional data analyses if necessary
- Advise on protocol modifications proposed by investigators or sponsors (e.g. inclusion criteria, trial endpoints or sample size)
- Decide whether to recommend the trial follow up should be stopped earlier
- Decide whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated either for everyone or for some treatment groups and/or some participant subgroups
- Consider the ethical implications of any recommendations made by the DMEC
- Monitor on-going risk benefit of patient data
- Monitor compliance with previous DMEC recommendations
- Maintain confidentiality of all trial information that is not in the public domain

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. 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, AEs and outcome data.

During the recruitment period, reports will be provided to the DMEC which will include information on SUSARs, SAEs, 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.

11.2 Definition of Adverse Events

The MHRA Good Clinical Practice Guide 2012 provides the definitions given in table

Table: 3 Terms and Definitions for AEs

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response in a participant to an investigational medicinal product, which is related to any dose administered to that participant.
Suspected unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the Summary of Product Characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the Investigator's Brochure (IB) relating to the trial in question.
Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction	Respectively, any AE, adverse reaction or unexpected adverse reaction that: • results in death • is life-threatening • requires hospitalisation or prolongation of existing hospitalisation* • results in persistent or significant disability or incapacity • consists of a congenital anomaly or birth defect 'Important medical events' may also be considered serious if they jeopardise the subject or require an intervention to prevent one of the above consequences. The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an inpatient admission regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.*

11.3 Eliciting Adverse Event Information

The PI or designee will record all directly observed AEs and those reported by the patient. In addition, the patient will be asked about AEs up to 28 days' post-surgery or on discharge from hospital if earlier. The PI or designee must assess all AEs for seriousness, causality, severity and if the AE is related to the study drug for expectedness.

11.4 Assessment of Seriousness and 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 or designated Investigator to have an unrelated, unlikely, 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:

Causality	Description
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

11.5 Grading of Severity of Adverse Events

The PI or designated investigator should make an assessment of severity for each AE according to the following categories:

- **Mild (Grade 1):** A reaction that is easily tolerated by the trial participant, causing minimal discomfort and not interfering with every day activities.
- **Moderate (Grade 2):** A reaction that is sufficiently discomforting to interfere with normal everyday activities.
- **Severe (Grade 3):** A reaction that prevents normal everyday activities.

- **Life Threatening (Grade 4):** A reaction that has life threatening consequences; urgent intervention indicated.
- **Death (Grade 5):** A reaction that results in death.

11.6 Assessment of Expectedness

The PI or designated investigator is required to make an assessment of expectedness of any AEs possibly, probably or definitely related to the IMP based on the relevant SmPC(s). Adverse reactions may be classed as either:

- **Expected:** The AR is consistent with the toxicity of the study drug listed in the SmPC.
- **Unexpected:** The AR is not consistent with the toxicity in the SmPC.

An AR may be described as 'unexpected' if it has occurred with greater frequency or severity that might otherwise have been expected.

11.7 Follow-up of Adverse Events

Patients, due to the nature of their surgery can develop complications such as respiratory complications which may result in a prolonged ICU/hospital stay. In such cases, follow up will be terminated at day 28 post-surgery or on discharge from hospital if earlier.

The follow up of the last patient will also be based on this criterion.

11.8 Recording of Adverse Events

Only AEs that are not related to underlying medical conditions are to be recorded and reported. All reportable AEs should be recorded in the patient medical notes and on the AE form within the EDC. An AR is an AE which is related to the administration of the study drug. All ARs must be reported on the AE form within the EDC.

11.9 Adverse Event Reporting

11.9.1 Adverse Event Reporting Period

The AE reporting period for this trial begins upon informed consent for the trial and ends 28 days post-surgery or until discharge from hospital if <28 days following the administration of the study drug. All AEs assessed by the PI as possibly, probably or definitely 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).

11.9.2 Adverse Event Reporting Requirements

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

11.9.3 Adverse Event Reporting

Prevention HARP-2 is recruiting a population that is already undergoing a major surgical intervention, 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 or surgical condition) should not be reported as AEs or SAEs. This will include

Wound infection, pneumonia

Cardiac arrhythmias

Primary and secondary clinical outcomes

Organ failure (excluding renal support for CK > 10 times ULN of local laboratory range)

Death related to surgical complications

All the above events will be documented but not reported as an AE/SAE. Death which is ascertained to be not related to surgical complications or progression of the primary or secondary outcomes should be reported as a SAE. SAEs will be evaluated by the PI for causality (i.e. their relationship to study drug) and expectedness. 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 EDC.

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 SmPC. 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.

11.9.4 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.

Prevention HARP-2 is recruiting a population that is undergoing a major surgical intervention, 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, as detailed above, 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

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 SmPC.

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 EDC and the SAE report completed and sent within 24 hours of the notification of the event occurring at site

The CTU is responsible for reporting SAEs to the Sponsors, and has been delegated reporting of SAEs to the REC and the MHRA 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 RECs within 15 days after the knowledge of such an event.

11.10 Data Monitoring

11.10.1 Data access

Prior to commencement of the study at each site, the PI will give 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 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.

11.10.2 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 on-going 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 Sponsor.

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 procedures.

On site monitoring visits during the study will check the completeness of patient records, the accuracy of data entered by sites into the clinical trial database (MACRO) against the source documents, the adherence to the protocol, procedures and GCP, and the progress of patient recruitment and follow up. Monitoring will also ensure that the study drug is being stored,

dispensed and accounted for according to specifications. The procedure for conducting on-site monitoring visits will be detailed in the monitoring plan.

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

The close-out procedures at each site will commence once the final patient enrolled has completed up to 28-day follow-up.

12 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.

12.1 Sponsorship

The BHSCT will act as Sponsor for the study and the CI will take overall responsibility for the conduct of the trial. Separate agreements will be put in place between the Sponsor, CI and each organisation who will undertake Sponsor delegation duties in relation to the management of the study.

12.2 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 REC.

A CTA will be obtained from the MHRA before the start of the trial.

12.2.1 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 trial manual will be provided for the sites participating in this study.

12.3 Protocol Amendments

The investigators will conduct the study in compliance with the protocol given approval/favourable opinion by the Ethics Committee and the regulatory authority. Changes to the protocol may require regulatory 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 sponsor will submit all protocol modifications to the competent authority/RECs for review in accordance with the governing regulations. Protocol compliance will be monitored by the CTU who will undertake site visits to ensure that the trial protocol is adhered to and that necessary paperwork (e.g. CRF's, patient consent) is being completed appropriately.

12.4 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). All members of the trial team will be required to have completed GCP training.

12.5 Protocol Compliance

A protocol deviation is defined as an incident which deviates from the normal expectation of a particular part of the trial process. Any deviations from the protocol will be fully documented on the protocol deviation form in the CRF.

A serious breach is defined as a deviation from the trial protocol or GCP which is likely to effect to a significant degree:

(a) The safety or physical or mental integrity of the subjects of the trial; or
(b) The scientific value of the trial

The PI or designee is responsible for ensuring that serious breaches are reported directly to the Sponsor within one working day of becoming aware of the breach.

In order to maintain confidentiality, all CRF's, questionnaires, study reports and communication regarding the study will identify the patients by the assigned unique trial identifier and initials only. Databases where information will be stored will be password protected. 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.

12.6 Post-trial Care

Patient will receive routine standard of care post-trial and no added care is planned.

12.7 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. The agreements put in place between the Sponsors and individual.

12.8 Data Access

Following the publication of the primary and secondary study outcomes, there may be scope for the CI in the study to conduct additional analyses on the data collected. In such instances the CI will discuss this with the TMG. In the event of publications arising from such analyses, those responsible will need to provide the CI with a copy of any intended manuscript for approval prior to submission. Authorship will need to take the format of "[name] on behalf of the Prevention HARP-2 Clinical Trial Group" or something similar which will be agreed by the TMG.

12.9 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 TMF will be held by the CTU within the BHSCT. On completion of the trial the TMF will be archived by the CTU and the ISF and study data will be archived by the PI at each site according to the applicable regulatory requirements and for up to 15 years as required by the BHSCT as Sponsors. Following confirmation from the Sponsor the CTU will notify the PI at each site 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.

12.10 Competing Interests

The research costs including the cost of the intervention were funded by HSC R&D Division via a NIHR clinician scientist fellowship. The CI and members of the TMG have no financial or non-financial competing interests and the members of the DMEC/TSC will be asked to

confirm that they have no conflict of interest. In the event that a DMEC/TSC member reports a conflict of interest, advice will be sought from the Sponsor.

13 DISSEMINATION/PUBLICATIONS

13.1 Publication Policy

The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org).

The results of the trial will initially be reported to the trial collaborators as the success of the trial depends on the collaboration of doctors, nurses and researchers from across the study sites.

The findings will also be presented at national and international meetings with open access abstracts on-line e.g. the American Thoracic Society annual meeting. We also aim to publish the findings in high quality peer-reviewed open access (via Pubmed) journals in accordance with the open access policies proposed by the leading research funding bodies. 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.

13.2 Authorship Policy

An author will be considered to be someone who has made a substantive intellectual contribution to the study. All investigators, Trial Statistician and relevant members of the Trial Management Group will potentially be co-authors. Collaborators will be acknowledged.

13.3 Data Sharing Statement

Requests for data sharing will be reviewed on an individual basis by the CI and TMG.

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15 APPENDICES

15.1 Table of Appendices

Appendix 1	The Berlin Definition of Acute Respiratory Distress Syndrome
Appendix 2	Postoperative pulmonary complications- Melbourne Group Scale
Appendix 3	Myocardial Infarction

15.2 Appendix I: The Berlin Definition of Acute Respiratory Distress Syndrome

The Berlin Definition of Acute Respiratory Distress Syndrome	
Acute Respiratory Distress Syndrome	
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities – not fully explained by effusions, lobar/lung collapse, or nodules
Origin of oedema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg. Echocardiography) to exclude hydrostatic oedema if no risk factor present
Oxygenation[b]	Mild – 200mmHg <PaO_2/FiO_2≤300mm Hg with PEEP or CPAP ≥ 5 cm H_2O[c]
	Moderate - 100mmHg <PaO_2/FiO_2≤200mm Hg with PEEP or CPAP ≥ 5 cm H_2O
	Severe - PaO_2/FiO_2≤100mm Hg with PEEP or CPAP ≥ 5 cm H_2O

Abbreviations: CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure

[a] Chest radiograph or computed tomography scan

[b] If altitude is higher than 1000m, the correction factor should be calculated as follows: [PaO_2/FiO_2 x (barometric pressure/760)]

[c] This may be delivered noninvasively in the mild acute respiratory distress syndrome group

15.3 Appendix II: Postoperative pulmonary complications- Melbourne Group Scale

Postoperative pulmonary complications as defined by Melbourne Group Scale

Based on the following 8 criteria. Post-operative pulmonary complication is defined by the presence of ≥ 4 criteria

1. Temperature > 38°C
2. White cell count > 11.2 or respiratory specific antibiotics
3. Physician diagnosis of pneumonia/chest infection
4. Chest X ray report of atelectasis/consolidation
5. Production of purulent (yellow/green) sputum differing from pre-operative status
6. Positive signs on sputum microbiology
7. SpO2 < 90% on room air*
8. Readmission to or prolonged stay (over 36 hours) on the intensive care unit or high dependency unit for respiratory problems

* or on ≥ 35% O_2 supplementation to maintain saturation > 94% which is equivalent to ≥ 4l via nasal cannula or ≥ 35% via other O_2 delivery devices

15.4 **Appendix III: Myocardial Infarction**

Myocardial infarction is defined by either

i) *Increase of at least one troponin value above the 99th percentile upper reference limit and one of the following criteria:

- symptoms of ischaemia

- new or presumed new significant ST segment or T wave ECG changes or new left bundle branch block

- development of pathological Q waves on ECG; radiological or echocardiographic evidence of new loss of viable myocardium or new regional wall motion abnormality

- identification of an intracoronary thrombus at angiography or autopsy

or

ii) **Myocardial infarction in non-cardiac surgery (MINS) criteria:

In evaluating MINS, troponin concentration should be measured daily for the first three days after surgery with Peak troponin T (TnT) ≥ 0.03 ng/ml considered as significant.

* Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Eur Heart J 2012; 33:2551–2567.

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