PHARLAP

A multi-centre randomised controlled trial of an Open Lung Strategy including Permissive Hypercapnia, Alveolar Recruitment and Low Airway Pressure in patients with acute respiratory distress syndrome.

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SYNOPSIS

Background	Acute respiratory distress syndrome (ARDS) is an inflammatory condition of the lungs, which is associated with high morbidity and mortality. Tidal volume and plateau pressure minimisation have been shown to decrease mortality in patients with ARDS. Open lung strategies, including higher positive end-expiratory pressure (PEEP) and recruitment manoeuvres, may provide an additional benefit, particularly if they are tailored for each patient. However, methodological limitations of previous studies may have hindered their ability to demonstrate a beneficial effect. A comprehensive open lung strategy (called PHARLAP) has been designed based on recent research, and this includes both tidal volume and plateau pressure limitation, as well as a staircase recruitment manoeuvre and individualised PEEP titration. In a pilot study this strategy was demonstrated to be safe and improved a range of physiological and inflammatory markers in patients with ARDS.
Aim	To investigate the clinical efficacy of the PHARLAP strategy compared to standard mechanical ventilation in ARDS patients.
Objectives	In a prospective, multi-centre, randomised controlled trial it will be determined whether PHARLAP ventilation increases ventilator free days compared to standard care.
Methods	340 adult patients who have developed ARDS within the last 72 hours (and within 10 days of commencing mechanical ventilation) will be enrolled in 25-30 intensive care units (ICUs) and randomly allocated to either the PHARLAP or a control ventilation strategy. PHARLAP strategy: Pressure control ventilation to maintain tidal volume 4-6 ml/kg and plateau pressure ≤ 30 cmH_2O while tolerating respiratory acidosis if pH > 7.15; daily staircase recruitment manoeuvre and individualised PEEP titration. Control strategy: Mechanical ventilation based on the ARDSnet protocol with tidal volume 6 ml/kg, plateau pressure ≤ 30 cmH_2O and FiO_2/PEEP titration according to a FiO_2/PEEP/oxygen saturation combination chart. This has been modified for Australian and New Zealand practice to allow pressure control and pressure support ventilation. A standardised weaning from mechanical ventilation guideline will be used in both groups.
Outcomes	The primary outcome is the number of ventilator free days (VFDs) at day 28. Secondary outcomes include physiological (PaO_2/FiO_2 ratio, static lung compliance), inflammatory (IL-6 & IL-8 in blood and BAL), clinical (safety, length of stay, mortality and quality of life at 6 months) and economic (cost effectiveness at 6 months) variables.

STUDY ADMINISTRATION STRUCTURE

Coordinating Centre

Australian and New Zealand Intensive Care Research Centre (ANZIC-RC), Department of Epidemiology and Preventative Medicine (DEPM) Monash University, Victoria, Australia

Responsibilities

- Overall management of the study including assistance with HREC applications
- Management of study budget and liaison with funding bodies
- Protocol and case report form (CRF) design and production
- Database design and management
- Protocol training of research coordinators and PHARLAP study team
- Preparation and arrangement of investigator payments
- Study set-up
- Randomisation
- Coordination of data entry and feedback of data enquiries
- Monitoring and close-out site visits
- Organisation of investigator meetings
- Serious adverse event notification
- Data analysis and collaboration on publications

Management Committee

Responsibilities

Overseeing all aspects of the study management including:

- Liaison with coordinating centre staff
- Liaison with steering committee
- Liaison with Australian & New Zealand Intensive Care Society Clinical Trials Group
- Liaison with Clinical Informatics and Data Management Unit
- Overseeing funding applications
- Overseeing disbursement & administration of funds
- Ensuring fiscal responsibilities are maintained
- Development and approval of final protocol and study materials
- Development and approval of data collection tools and methods
- General study management issues

Members

• A/Prof Yaseen Arabi	Chairman, Intensive Care Department, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
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- Ms Lynne Murray — Research Manager, ANZIC-RC, Monash University
- Prof Alistair Nichol — Professor, ANZIC-RC, Monash University
- Ms Rachael Parke — Research Co-ordinator, Auckland City Hospital
- Prof David Tuxen — Senior Intensivist, The Alfred Hospital
- Ms Shirley Vallance — Research Manager, The Alfred Hospital

Training and Education Committee

Responsibilities

- Study start-up meetings
- Protocol training to research coordinators and site investigators

Members

- Ms Victoria Bennett
- Dr Carol Hodgson (co-chair)
- Dr Shay McGuinness
- Ms Rachael Parke
- Prof David Tuxen (co-chair)

Steering Committee

Responsibilities

- Oversight and advisory role
- Data analysis, collaboration and approval of study publications

Members

- Management committee (as above)
- Associate Investigators*

*Local representatives to be appointed once sites confirmed

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Endorsement

The PHARLAP study has been endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG).

MANAGEMENT COMMITTEE AUTHORISATION

We the management committee have read the attached protocol and authorize it as the official protocol for the study entitled "A multi-centre randomised controlled trial of an Open Lung Strategy including Permissive Hypercapnia, Alveolar Recruitment and Low Airway Pressure in patients with acute respiratory distress syndrome".

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LAY DESCRIPTION

Some people develop the condition called acute respiratory distress syndrome (ARDS). This is a condition where the lungs have become injured from one of a number of various causes, and do not work as they normally do to provide oxygen and remove carbon dioxide from the body. This can lead to a reduced amount of oxygen in the patient's bloodstream. Patients with ARDS are admitted to the intensive care unit (ICU) and need help with their breathing by being connected to a ventilator (breathing machine). ARDS can lead to injury in other organs of the body causing other problems but also death.

Over the past few years, reducing the size of each breath delivered by the ventilator in conjunction with the use of an occasional sustained deep breath called a "recruitment manoeuvre" have been used to try to prevent further damage to the lungs in people with ARDS. This ventilator strategy (termed the PHARLAP strategy) has been shown in a small research study to have some beneficial effects without causing any obvious harm, when compared to a current best practice ventilator strategy. The main beneficial effects of the PHARLAP strategy were to increase the amount of oxygen in the blood and to reduce markers of inflammation (the body reacting to a disease process) in the body. This study was too small to make a strong conclusion, so this study will be much larger and will assess whether patients who have developed ARDS are better off when we use the PHARLAP strategy. Three hundred and forty patients will be enrolled into this study in multiple ICUs across Australia and New Zealand.

ABBREVIATIONS

A/C = assist/control ventilation

AKI = acute kidney injury

ANZIC-RC = Australian & New Zealand Intensive Care Research Centre

ANZICS CTG = Australia & New Zealand Intensive Care Society Clinical Trials Group

ARDS = acute respiratory distress syndrome

ARDSnet = acute respiratory distress syndrome network

bpm = beats per minute

CIDMU = clinical informatics data management unit

cmH_2O = centimetres of water

CPAP = continuous positive airway pressure

CPMP = committee for proprietary medicinal products

CT = computed topography

CXR = chest X-ray

ECMO = extra corporeal membrane oxygenation

FiO_2 = fraction of inspired oxygen

GCP = good clinical practice

HREC = Human Research and Ethics Committee

ICH = international conference on harmonisation

ICU = intensive care unit

IL-6 = plasma interleukin 6

IL-8 = plasma interleukin 8

LRM = lung recruitment manoeuvres

mmHg = millimetres of mercury

ml/kg = millilitres per kilogram

NHMRC = National Health and Medical Research Council

OLS = open lung strategy

PBW = predicted body weight

PEEP = positive end expiratory pressure

PEEPi = intrinsic positive end expiratory pressure

PaO_2 = partial pressure of oxygen in arterial blood

$PaCO_2$ = partial pressure of carbon dioxide

Paw = peak airway pressure

PSV = pressure support ventilation

RCT = randomised controlled trial

SAE = serious adverse event

SaO_2 = oxyhaemoglobin saturation measured in arterial blood

SBP = systolic blood pressure

SIMV = synchronised intermittent mandatory ventilation

SOFA = sequential organ failure assessment score

SRM = staircase recruitment manoeuvre

TNF = tumour necrosis factor

VFDs = ventilator free days

X-ray = radiograph

BACKGROUND & RATIONALE

Acute Respiratory Distress Syndrome

Acute Lung Injury (ALI) and the more severe variant ARDS are inflammatory conditions of the lung parenchyma[1,2]. They cause impaired gas exchange and hypoxaemia with concomitant systemic inflammatory mediator release, frequently causing multiple organ failure and death[1,2]. The Australian incidence of ARDS, from a survey of 21 ICUs in the late 1990's, was 28 cases per 100,000 per annum, with a 34% mortality rate[3]. More recently (2009), the ANZICS CTG Point Prevalence Investigators completed a point prevalence study demonstrating 42 out of 678 Australian ICU patients (6%) studied that day had ARDS. In a prospective, one month observational study of mechanically ventilated patients in 27 Australian ICUs in 2010, 27 out of the 650 patients studied (4%) developed ARDS. Of these 27, 6 (22%) had died and 10 (37%) remained hospitalised (5 (19%) in ICU) at day 28 (unpublished; NCT01093482). Finally, during the recent winter H1N1 2009 influenza pandemic, 49% of the patients admitted to Australian ICUs with influenza developed ARDS/pneumonitis[4], 17% died in hospital and many required hypoxaemic rescue therapies[5], such as extracorporeal membrane oxygenation (ECMO). Many of these patients were young (median age <60 years)[4-7]. These results are consistent with international experience[8,9] that has shown that despite best supportive care, ARDS is common, and is associated with significant mortality and morbidity (prolonged mechanical ventilation and use of expensive hypoxaemic rescue therapies)[7,8,10]. The hospital costs are also high with the average cost of each ARDS/pneumonitis patient with H1N1 influenza being AUD $56,479, twice that of those without ARDS, and significantly higher for those requiring hypoxaemic rescue therapies (AU$160,735 for ECMO)[11]. Based on this, ARDS patients cost Australia at least $20,000,000 in hospital expenses alone per annum. When these financial, mortality and morbidity costs are added to the significant functional and quality of life burden, which is still demonstrable one-year post-ARDS[12], the societal impact of ARDS is significant. Any intervention that impacts on mortality, time on mechanical ventilation and the need for expensive rescue therapies is likely to have important human, social and financial benefits.

ARDS pathophysiology and the effect of mechanical ventilation on organ failure

ARDS is associated with diffuse alveolar damage and increased influx of fluid into the alveoli13. Computed tomography (CT) studies in ARDS demonstrate that the apparently homogeneous lung infiltrate seen on frontal chest x-ray (CXR) is actually heterogeneous, with the densities concentrated primarily in the most dependent regions (Fig. 1, left)[13].

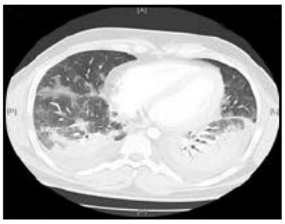
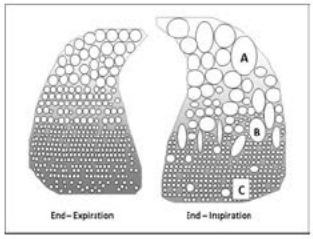


Figure 1. CT of supine ARDS patient (left, reproduced with permission) showing atelectasis and oedema in the dependent lung regions.

Schematic diagram (right) of ARDS lung A) overinflated, B) alveoli opening and closing with each breath and C) non-aerated tissue.



While mechanical ventilation is a lifesaving intervention by maintaining satisfactory gas exchange, it can augment or even initiate lung injury. Mechanical ventilation can damage the lung via a number of mechanisms: alveolar strain due to high tidal volumes (volutrauma) and ventilation pressures (barotrauma) (Fig. 1 (zone A)) and shear stress-induced injury caused by unstable alveoli recruiting and de-recruiting with each breath (atelectrauma, Fig. 1 (zone B))[14]. Chronic collapse injury (Fig. 1 (zone C))[14] is not directly due to mechanical ventilation but has the potential for improvement with mechanical ventilation. These repetitive mechanical assaults promote a deleterious pulmonary and systemic inflammatory injury, called biotrauma[15]. ARDS patients who die often succumb not to hypoxaemia but to multiple organ failure secondary to the ongoing ventilator induced injury promoting the deleterious systemic inflammatory injury (biotrauma)[1].

What are the attributes of the "ideal" mechanical ventilation strategy in ARDS

The "ideal" ventilator strategy in ARDS aims to maintain gas exchange and to reduce ventilator induced injury in each of these distinct pathological zones[13,14,16] (Fig.1). Volume and pressure limitation to reduce alveolar strain injury in Zone A (Fig. 1) has been shown to significantly reduce mortality in ARDS[16,17]. However this strategy[16,17] may aggravate collapse/re-expansion injury in Zone B (Fig. 1) and fails to address the non-aerated Zone C[14] (Fig. 1), which leads to prolongation of mechanical ventilation, organ failure and mortality[1]. To address this, two large randomised trials using moderate intensity lung recruitment manoeuvres (LRM; maximum alveolar pressure of 40 cmH_2O for ≤ 40 sec) and meta-analyses[18,19] of trials using similar LRMs have been conducted, and none have found a significant benefit to mortality. As a result, lung recruitment is not a routinely used part of ARDS management outside of clinical trials. The hypothesis of the PHARLAP study is that an "open lung strategy" (OLS) with a higher intensity LRM combined with improvements in several other key ventilator strategy components may be more effective than current volume and pressure limitation mechanical ventilation. This open lung strategy includes A) optimal LRMs with individualised positive end-expiratory pressure (PEEP) titration and B) further limitation of tidal volumes and airway pressures, facilitated by C) a tolerance of hypercapnia.

Lung recruitment manoeuvres + optimal PEEP

Only one study of a LRM with "higher" PEEP has demonstrated a survival advantage[17], and this benefit was largely attributed to the lower tidal volume (now standard practice) also used in this strategy. Since then, three large RCTs using protocolised higher PEEP levels, with low tidal volume, with or without LRMs, failed to demonstrate a survival advantage but decreased severe hypoxaemia[7], decreased the need for hypoxaemic rescue therapies[7] and increased ventilator free days (VFDs)[20]. However, the ability of these studies to have realised the true potential of the open lung strategy and to have demonstrated a cumulative advantage on top of tidal volume and pressure limitation was negated by methodological limitations:

Inadequate pressure and duration of the recruitment manoeuvre

A progressive (over many minutes) static inflation and deflation of the lung to recruit the lungs and then set the "optimal" PEEP was initially studied[17]. This "super-syringe" technique has fallen out of favour due to the significant requirements of sedation and paralysis and the associated haemodynamic compromise. Subsequent studies therefore used a more conservative LRM using 40 cmH_2O pressure for 40 seconds (a 40/40 LRM)[7,21], which may deliver too little pressure for too short a time period to be maximally effective[18,22,23]. Animal studies in ARDS have demonstrated a stepwise lung recruitment manoeuvre (SRM, see Figure 2) was the most effective at improving oxygenation[24]. The clinical efficacy and safety of this SRM has been established in ARDS patients with a sustained positive effect on oxygenation and CT characteristics[25]. In a second study, a similar SRM improved PaO_2/FiO_2 ratio, shunt fraction, compliance and lung field radiolucency on CXR sustained for at least one hour after the SRM in 18 of 20 (90%) patients[26]. Based on these previous studies, only 46-54% of patients who responded to the SRM may have fully responded with a 40/40 LRM[17], reinforcing suggestions that previous RCTs[7,21] used a LRM of insufficient duration and intensity[20]. The studies of this SRM reported some transient haemodynamic effects during the SRM, but there were no clinically significant consequences[25,26].

Figure 2

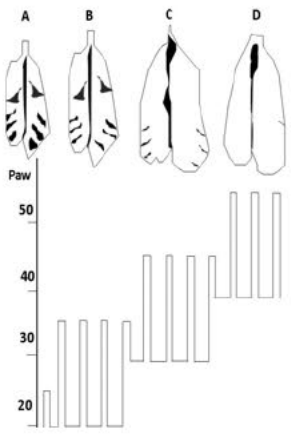


Figure 2: The SRM (*Left*). The PEEP is stepwise increased from baseline to 20, then 30 and finally 40 cmH_2O with continuing pressure control ventilation (15 cmH_2O). Picture A) de-recruited, B→C) progressively recruiting and D) fully recruited lung. Paw; Peak airway pressure.

Figure 3

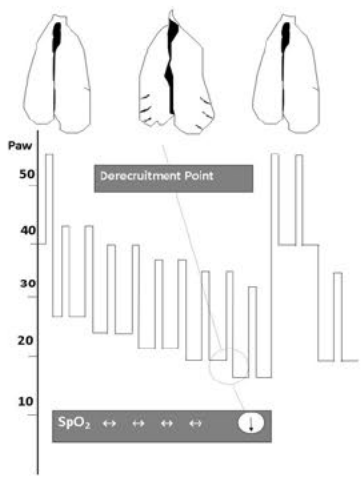


Figure 3: **PEEP titration manoeuvre** (*Right*). PEEP is stepwise reduced until a sustained drop in SaO_2, the de-recruitment point (Picture D→E). A LRM is then required to re-open these collapsed alveoli and then PEEP is set at the step above the de-recruitment point (Picture F). Paw; Peak airway pressure.

Inadequate and untitrated PEEP following recruitment manoeuvre

It is likely that the level of PEEP set after an LRM is important and this should be the minimum required to maintain PEEP-dependent re-opening of atelectatic areas while avoiding PEEP-induced lung over-inflation[6,14,20,25,27,28]. How best to achieve this has been one of the most vexed questions in critical care[27,28]. Various techniques have been proposed, including a) pulmonary mechanics (i.e. using super-syringe, plateau pressure etc)[17,29,20], b) CT guided[27,32] and c) FiO_2/PEEP algorithms[6,16]. However, these techniques have been criticised because they are either clinically impractical, necessitate deep sedation or paralysis, lead to large physiological perturbations, introduce dangers related to radiation exposure and patient transport, lack sound physiological rationale, or are insensitive to heterogeneous pulmonary lesions (the presence of recruitable vs non-recruitable alveoli) and may be injurious (PEEP induced over inflation)[23,30,12,27]. Oxygen saturation measured by pulse oximetry is a familiar, simple and a physiologically sound "yard stick", for clinicians to determine the minimum PEEP needed to maintain recruitment. In brief, the fraction of inspired oxygen (FiO_2) is adjusted to achieve a saturation of 90-92% (the "shoulder" of the oxyhaemaglobin dissociation curve), a point where even small increases in alveolar collapse (de-recruitment) will increase pulmonary shunt and reduce oxygenation as detected by a fall in saturation[22,26]. After adequate recruitment (i.e. the SRM), PEEP is reduced in incremental steps until a drop in saturation occurs, the de-recruitment point (Fig. 3). A further LRM is then performed to re-expand these newly collapsed alveoli and the PEEP is 'set' at the step above the de-recruitment point (i.e. 2.5 cmH_2O higher, Fig 3). This approach has been demonstrated to lead to sustained improvements in ARDS patients[25,31]. While Huh et al demonstrated that PEEP titration resulted in improved oxygenation levels and was safe, it did not affect mortality[32]. Unfortunately, this small study seemed likely to have been hindered by an inadequate LRM (max PEEP 25 cmH_2O) and a PEEP titration approach which permitted insufficient levels of PEEP (i.e. <15 cmH_2O) post LRM[14].

Higher plateau pressures in the prior OLS high PEEP groups[6,7,20], due to similar tidal volume in both groups may also have confounded detection of the potential beneficial effects. In addition, OLS may be beneficial in ARDS but not in ALI patients[33], suggesting the previous inclusion of ALI patients in prior studies may have diluted their potential to detect a protective effect[6,7,17].

Even lower tidal volume and airway pressures

Amato et al demonstrated that the use of lower tidal volume (6 ml/kg) and plateau airway pressures to minimise alveolar strain reduced mortality compared to higher tidal volume (12 ml/kg)[17], a finding confirmed in the multi-centre ARDSnet study[16]. Laboratory work[34] and recent clinical evidence, including an unpublished meta-analysis by Amato (personal communication) demonstrate a correlation between plateau pressure (even < 30 cmH_2O) and mortality in ARDS. This suggests that even the current "non-injurious" tidal volumes and airway pressures which are commonly accepted may be too high and augment lung injury. Plateau airway pressures of about 25–28 cmH_2O appear to be safer[34,35]. Reducing tidal volume and plateau pressure therefore aims to further minimise alveolar strain, especially in conjunction with an OLS encouraging higher PEEP levels.

Permissive hypercapnia to facilitate reduced tidal volume and airway pressures

The tolerance of hypercapnia to limit repetitive alveolar strain (i.e. tidal volume and plateau pressure) has been advocated by many[36,37]. Hypercapnia may also be protective independent of any changes in tidal volume[38-40]. Furthermore, hypercapnia is well tolerated by the critically ill[36,37] and the benefit of tightly controlling CO_2 is questionable and may even augment lung injury[41]. The ideal OLS should tolerate hypercapnia to minimise alveolar strain.

PHARLAP pilot randomised controlled trial

A pilot trial was conducted to examine the effectiveness and safety of such an Open Lung Strategy, which included permissive hypercapnia, stepwise alveolar recruitment manoeuvres (SRM) with PEEP titration (titrating against oxygen saturation) and low airway pressure (PHARLAP)[31]. ARDS patients were randomised to PHARLAP (n=10) or control ventilation (n=10) strategies. By design, the PHARLAP group had higher levels of PEEP, but not plateau pressures, than the control group.

Compared to the control group the PHARLAP strategy significantly improved:

i) Physiological markers: oxygenation (PaO_2/FiO_2 ratio) and pulmonary mechanics (static lung compliance) over 7 days, suggesting sustained increases in alveolar recruitment.

ii) Systemic inflammatory markers: greater reduction from baseline to day 7 plasma interleukin-8 (IL-8) and tumour necrosis factor-alpha (TNFα) suggesting reduced biotrauma.

iii) Clinical/patient-centred outcomes: Non-significant improvements in VFDs (14.8 v 11.8 days), ICU and hospital length of stay and reduced use of hypoxaemic rescue therapies.

Summary: The PHARLAP ventilation strategy improved lung function (oxygenation, compliance and the use of hypoxaemic rescue therapies), reduced systemic inflammation (cytokine concentrations) and was associated with non-significant improvements in patient-centred outcomes (although was significantly underpowered to detect a difference in these outcomes).

Feasibility of an Australasian trial of the PHARLAP strategy in ARDS

The ANZICS CTG has the proven ability to conduct large-scale, multi-centre, clinical trials in critically ill patients[42] and this study has been endorsed by the ANZICS CTG.

The investigators have an established track record in conducting world-leading studies involving ARDS patients, published in the highest impact journals (NEJM, JAMA, AJRCCM)[3,4,5,7,17]. In addition, they have extensive experience conducting large-scale randomised controlled trials of complex critical care interventions (SAFE[43], Feeding Guidelines study[44], DECRA[45], ARISE (NCT00975793) and POLAR (NCT00987688)). They have conducted a number of laboratory[38,39] and clinical studies[17,25,26,31] demonstrating the safety and efficacy of the components of the PHARLAP study.

The feasibility of the PHARLAP strategy has been tested in a separate study investigating the adherence to the PHARLAP strategy protocol at Prince Charles Hospital (Qld) and Flinders Medical Centre (SA) (ACTRN12611000665932).

A one-month prospective observational study in 2010 determined that 27 patients met the PHARLAP inclusion criteria; an average of 1 patient per site per month in Australia and New Zealand. This recruitment rate is consistent with previous experience conducting observational[3] and interventional[7,31], ventilation studies in our region. Assuming a recruitment rate of 50% (including refusal of consent), we aim to recruit 150 patients per annum, with 25 sites, resulting in a 2¼ year enrolment period.

Significance

There is substantial experimental evidence, biological rationale, and supportive clinical evidence to suggest the efficacy of the PHARLAP ventilation strategy in ARDS. However, mostly because of concern that SRM's and high PEEP may cause barotrauma and haemodynamic instability in critically ill patients, previous trials may have been sub-optimally designed to determine the true efficacy of such an OLS. The PHARLAP strategy is more intensive, more individual patient tailored and at least as safe as previously studied open lung strategies. In addition, the PHARLAP strategy can be delivered by almost any clinician using any conventional mechanical ventilator and if proven effective and safe, would be highly applicable for widespread use (including the developing world). Given the significance and cost of ARDS, the possible benefits of this strategy, the growing number of recommendations for the use of a LRM with elevated levels of PEEP[18,19,46], this study is an important undertaking. The trial will determine whether the PHARLAP ventilation strategy is effective in increasing ventilator free days in patients with ARDS. If the PHARLAP strategy is proven to improve ventilator free days it will provide a strong impetus to conduct an international phase III RCT to determine the effects of this strategy on mortality.

OBJECTIVES

Aim

To determine the efficacy of the PHARLAP strategy compared to a control ventilation strategy in increasing ventilator free days assessed during the 28 days post randomisation.

Hypothesis

The PHARLAP strategy group will have a higher number of ventilator free days at day 28 than the control group.

STUDY OUTCOME MEASURES

Primary outcome

- Number of ventilator free days at day 28 post randomisation

Secondary outcome

- Physiological outcomes:
  - PaO_2/FiO_2 ratio
  - Static lung compliance
- Inflammatory outcomes:
  - Baseline to day 3 change in IL-8 and IL-6 concentrations in broncho-alveolar lavage fluid
  - Baseline to day 3 change in IL-8 and IL-6 concentrations in plasma
- Clinical/patient-centred efficacy outcomes:
  - Use of rescue therapies for severe hypoxaemia – inhaled nitric oxide, inhaled prostacyclin, prone positioning, high frequency oscillatory ventilation and extracorporeal membrane oxygenation (ECMO)
  - Incidence of acute kidney injury (AKI)
  - ICU and hospital length of stay
  - Quality of life assessment (SF-36v2 and EQ-5D) at 6 months
  - Mortality at ICU/hospital discharge, 28 days, 90 days and 6 months
  - Cause of death
- Safety outcomes:
  - Barotrauma
  - Severe hypotension
  - Serious adverse effects (SAEs)
- Economic outcomes:
  - Cost effectiveness analysis at 6 months (based on EQ-5D)

Determination of primary outcome

The primary outcome is the number of ventilator free days at day 28 post randomisation, and will be defined as the total number of days from day 1 to day 28 on which a patient is alive and receives no assistance from mechanical ventilation, if any period of ventilator liberation lasts at least 48 consecutive hours. Study day 1 is the day of enrolment and will continue until the end of the daily ICU chart used at that site, or the end of the calendar day if electronic data collection systems are used. If patients are on mechanical ventilation for any portion of the study day they will be classified as being on mechanical ventilation for that entire study day. To be considered truly liberated from mechanical ventilation, the patient will need to have at least 48 consecutive hours where they are liberated from mechanical ventilation. This means that if, for example, they have 47 consecutive hours liberated from mechanical ventilation and then receive mechanical ventilation, none of this time will be considered as ventilator free. But if, for example, they have 49 consecutive hours liberated from mechanical ventilation and then receive mechanical ventilation, all of this time will be considered as ventilator-free, to contribute to classification of the ventilator-free status for each study day. Non-invasive mechanical ventilation will not be considered assistance if it is provided by face or nasal mask, but will be considered assistance if it is provided by tracheostomy. Any patient who dies before weaning from mechanical ventilation will be allocated the value of 0 ventilator free days. Any patient who dies after weaning from mechanical ventilation (ie. they have at least 48 consecutive hours off mechanical ventilation) but before day 28 will not have the days after their death until day 28 considered as a ventilator free day.

STUDY METHODOLOGY

Study outline

A phase II, multi-centre, prospective, randomised controlled trial.

Study population

Patients meeting all the inclusion and none of the exclusion criteria in the ICU will be eligible for enrolment.

Inclusion criteria

Adult ICU patients who meet all of the following criteria:

- Currently intubated and receiving mechanical ventilation
- Within 72 hours of mechanical ventilation for a diagnosis of ARDS (moderate and severe) based on the Berlin definition[47]
    - Within 1 week of a known clinical insult or new or worsening respiratory symptoms
    - Bilateral opacities on CXR which are not fully explained by effusions, lobar/lung collapse or nodules
    - Respiratory failure not fully explained by cardiac failure or fluid overload
    - PaO_2/FiO_2 < 200 mmHg with PEEP ≥ 5 cmH_2O

Exclusion criteria

- > 72 hours since diagnosis of ARDS
- > 10 days of continuous mechanical ventilation
- < 16 years of age
- Barotrauma (pneumothorax, pneumomediastinum, subcutaneous emphysema or any intercostal catheter for the treatment of air leak)
- Significant chest trauma i.e. multiple rib fractures
- Active bronchospasm or a history of significant chronic obstructive pulmonary disease or asthma
- Clinical suspicion for significant restrictive lung disease (history of pulmonary fibrosis or suggestive pulmonary function tests)
- Moderate or severe traumatic brain injury, the presence of an intracranial pressure monitor, or any medical condition associated with a clinical suspicion of raised intracranial pressure
- Unstable cardiovascular status defined as sustained heart rate < 40 or > 140 bpm, ventricular tachycardia, or SBP < 80 mmHg
- Pregnancy
- Receiving ECMO
- Receiving high frequency oscillatory ventilation
- Death is deemed imminent and inevitable
- The treating physician believes it is not in the best interest of the patient to be enrolled in the trial
- Consent not obtained or refused by patient's legal surrogate

Patient screening

Patients will be screened for eligibility criteria in 25-30 ICUs in Australia and New Zealand.

Informed consent

Patients will be unable to provide prospective informed consent, as they will be sedated and receiving mechanical ventilation. Informed consent will be obtained from the most appropriate Person Responsible, in accordance with section 4.4.10 of the NHMRC National Statement, and with variations according to state and territory legislations (and also as appropriate for New Zealand). Delayed consent for long-term follow up will be sought from the participant when they have suitably recovered capacity.

Enrolment and randomisation

Site personnel will enrol patients using an internet-based system hosted by the ANZIC Research Centre. Randomisation to either the PHARLAP group or the control group will be by permuted blocks and stratified for centre and for the cause of ARDS (direct or indirect)[48].

Co-enrolment

Co-enrolment of patients into other interventional studies will be decided by the PHARLAP and the co-enrolling study management committees on a case-by-case basis. Participants can be co-enrolled in observational studies.

PARTICIPATING STUDY SITES

To be confirmed

- Albury Wodonga Health
- CVICU, Auckland City Hospital
- DCCM, Auckland City Hospital
- Austin Hospital
- Barwon Health (Geelong Hospital)
- Flinders Medical Centre
- John Hunter Hospital
- King Abdulaziz Medical City for National Guard (Riyadh)
- Lyell McEwin Hospital
- Middlemore Hospital
- Nepean Hospital
- Northern Hospital
- Launceston
- Prince Charles Hospital
- Royal North Shore
- Royal Prince Alfred
- St Vincents Hospital (Dublin)
- The Alfred Hospital
- Wellington Hospital
- Wollongong Hospital

STUDY PROCEDURES

Commencement of mechanical ventilation strategy

Patients in both groups should be commenced on the assigned mechanical ventilation strategy as soon as possible (but no later than 4 hours) after randomisation.

Prior to changing the pre-randomisation mechanical ventilation settings to the assigned strategy, 3 tasks need to occur in the following order in both groups of patients:

1. Predicted body weight should be estimated.
2. Static respiratory compliance should be measured (see below).
3. Specimens of blood and BAL should be collected (see below) – after static respiratory compliance has been measured.

Estimation of predicted body weight:

Before setting up the ventilator strategy, the patient's predicted body weight must be determined. This should be estimated using a formula which requires height[49] (Appendix 1). If there has been no recent (last few days) measurement of height, the height should be estimated using a formula which requires measurement of the demi-arm span (Appendix 1).

Measurement of static respiratory compliance:

- The patient should be adequately sedated (no spontaneous breaths).
- An expiratory pause of 5 seconds should be set to measure intrinsic PEEP (PEEPi). If the 5 second pause can not be achieved (because the next breath occurs before the end of the pause), a shorter pause should be set.
- Total PEEP is calculated as PEEPi + set PEEP.
- The expiratory pause should be removed, and 30 seconds waited, before a 0.5 second inspiratory pause should be set to measure plateau pressure.
- Within the same breath, expired tidal volume and plateau pressure should be measured.
- Static respiratory compliance should be calculated as tidal volume / (plateau pressure – total PEEP).

Collection of specimens at baseline:

Patients in both groups should have specimens of blood and bronchoalveolar lavage (BAL) fluid collected prior to commencement of the assigned mechanical ventilation strategy.

The blood specimen should be collected from the arterial line and sent with the BAL specimen to the site's pathology department for appropriate spinning and storage. These will be sent in batches to Flinders Medical Centre for measurement of IL-6 and IL-8 levels in both blood and BAL.

To perform the BAL, we recommend using a bronchoscopic method. Alternatively a non-bronchoscopic technique using the KimVent BAL Cath (Bronchial Aspirate Sampling Catheter) can also be used. There are two sizes of KimVent BAL Caths – 13F is recommended for a size 7cm ETT and smaller and 16F is recommended for a size 7.5cm ETT and larger. These will be provided to all sites by the ANZIC-RC. Whichever method is used, at least 10 ml of BAL fluid should be collected. A right-sided BAL is preferred for consistent sampling.

Appendix 2 includes instructions on how to collect the specimen if a bronchoscopic method is used. It also includes instructions on how to perform the non-bronchoscopic technique using the KimVent BAL Cath to collect the BAL specimen.

If the patient has been assigned to the PHARLAP group, this procedure should now be followed as soon as possible (but no later than 4 hours after randomisation) by a combined open lung procedure (see below). Satisfactory haemodynamic resuscitation may also be required before 4 hours after randomisation.

If it is not feasible to collect a BAL sample because of limited resources to perform the bronchoscopy or the Investigator is unfamiliar with the use of the KimVent BAl cath or it may cause undue delay in recruitment then

a BAL sample is not required to be collected once enrolled. We understand that this may occur from time to time. However, every attempt should be made to collect the blood sample on all patients.

Control group mechanical ventilation

Initial commencement of mechanical ventilation in the control group

Mode: After randomisation, patients should be commenced in either Assist/Control (A/C) or Synchronised Intermittent Mandatory Ventilation (SIMV). All patients should be commenced in controlled rate ventilation, even if this requires additional sedation and/or neuromuscular blocking drugs. The preferred mode is Volume Control as follows.

Tidal Volume: The tidal volume should be set at 6 ml/kg predicted body weight (PBW). The initial respiratory rate should be determined by aiming to deliver similar minute ventilation to the pre-randomisation settings. The maximum rate is 35 breaths/minute.

Plateau Pressure: The plateau pressure aim is ≤ 30 cmH_2O. If the plateau pressure is > 30 cmH_2O, the tidal volume should be reduced, but to no less than 4 ml/kg PBW.

FiO_2 and PEEP: The FiO_2 and PEEP should be set using the following table of allowable FiO_2 and PEEP combinations as a guide. The initial setting should be the combination of FiO_2 and PEEP that is closest to the pre-randomisation settings. The SaO_2 aim is 90-95% using the lowest FiO_2/PEEP combination to meet this goal. The PEEP level in this table represents the PEEP level set on the ventilator, not total or measured PEEP. The settings should be as far to the left of this chart as possible, thereby using the lowest combination of FiO_2 and PEEP possible while maintaining oxygenation within the target range. If the patient has a significant desaturation, it is permissible to rapidly increase the PEEP/FiO_2 from left to the right of the chart as quickly as required to achieve a satisfactory oxygen saturation, then titrate to achieve a SaO_2 90 – 95%.

When both SaO_2 and PaO_2 measures are available and discordant, PaO_2 should take precedence.

F_iO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP (cmH_2O)	5	5	8	8	10	10	10	12	14	14	14	16	18	18-24

pH: The arterial pH goal for control group patients is pH 7.30-7.45. However there is **no actual $PaCO_2$ target and it is more important to maintain a tidal volume less than 6 ml/kg and a plateau pressure < 30 cmH_2O.**

Acidaemia is permitted unless it is considered clinically relevant, in which case consider the following;

- If pH 7.15-7.30 - increase the set mechanical ventilator rate up to a maximum of 35 breaths/minute or until pH > 7.30 or $PaCO_2$ < 25 mmHg.
- If pH < 7.15 - increase the set mechanical ventilator rate, up to a maximum of 35 breaths/minute.
- If pH remains < 7.15 - tidal volume can be increased in 1 ml/kg steps until pH > 7.15 (Pplat target of 30 may be exceeded). Bicarbonate may be administered if felt clinically indicated. NMB may be administered if felt clinically indicated.
- Other mechanical ventilation strategies may be considered, but only after a dose of a neuromuscular blocking drug (in addition to suggestions for pH < 7.15). If the acidosis is predominantly metabolic, continuous renal replacement therapy may be required at this point.

If pH > 7.45 **and this is considered clinically relevant** we suggest decreasing the set mechanical ventilator rate (if possible) or decreasing plateau pressure by decreasing tidal volumes (no less than 4ml/kg PBW).

Alternative mode: Other modes may be considered as a preference by the clinician or because of ventilator dysynchrony in A/C volume controlled ventilation. If the main problem is ventilator dysynchrony, the patient should first have increased sedation and NMB may be administered if felt clinically indicated. Pressure Control mode may be used to deliver rapid inspiratory flow rates which may improve patient-ventilator interaction., although Volume Control mode is preferred. When Pressure Control is used, the inspiratory pressure should be set to achieve a tidal volume of approximately 6 ml/kg PBW. Plateau pressure in Pressure Control mode is considered to be the total pressure (ie. the sum of set inspiratory pressure + PEEP). If the total pressure is ≥ 30 cmH_2O, the inspiratory pressure should be reduced, but to no less than a setting that delivers a tidal volume of

approximately 4 ml/kg PBW. **Whilst Pressure Control mode is being used, tidal volumes should be carefully monitored (including the use of mechanical ventilator alarms) with the aim that these remain approximately 6 ml/kg PBW.**

Neuromuscular blocking drugs: Neuromuscular blocking drugs should be used as judged appropriate by the treating clinician and their current unit policies.

Ongoing mechanical ventilation in the control group

Goals: The goals of mechanical ventilation should always remain as follows:

- Tidal volume: ≤ 6 ml/kg PBW
- Plateau pressure: ≤ 30 cmH_2O (if plateau pressure ≥ 30 cmH_2O, reduce tidal volume to 4-6 ml/kg)
- Breath rate: ≤ 35 breaths/minute
- pH: 7.30-7.45 (do not aim for a specific $PaCO_2$)
- SaO_2: 90-95% (if PaO_2 is available, the aim for this is 60-80 mmHg). When both SaO_2 and PaO_2 are available and discordant, PaO_2 should take precedence.

Titrating the FiO_2 and PEEP: The FiO_2 and PEEP should be set using the table of allowable FiO_2 and PEEP combinations as a guide. The PEEP level in this table represents the PEEP level set on the ventilator, not total PEEP. The settings should be as far to the left of this chart as possible, thereby using the lowest combination of FiO_2 and PEEP possible while maintaining oxygenation within the target range.

If the SaO_2 is < 90% (or PaO_2 < 60 mmHg, if available), the patient should be changed to the FiO_2 and PEEP combination to the right of the current settings. If the patient has a significant desaturation, it is permissible to rapidly increase the PEEP/FiO_2 from left to the right of the chart as quickly as requiredto achieve a satisfactory oxygen saturation, then titrate the PEEP/FiO_2 to achieve a SaO_2 90 – 95%.

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP (cmH_2O)	5	5	8	8	10	10	10	12	14	14	14	16	18	18-24

If the SaO_2 is > 95% (or PaO_2 > 80 mmHg, if available), the patient should be changed to the FiO_2 and PEEP combination to the left of the current settings. If this leads to a reduction in PEEP, it is preferable not to reduce the PEEP again **before 4 hours have passed**.

Ventilation during patient transfers: Mechanical ventilation should continue to adhere to this control group strategy during patient transfers (to diagnostic or therapeutic procedures outside the ICU) where possible. However if the patient receives mechanical ventilation using either a manual (hand-bagging) circuit or a transport ventilator that is not practically able to deliver the control group mechanical ventilation settings, patients may be ventilated using alternative means whilst away from the ICU. Resumption of control group mechanical ventilation should occur as soon as possible after the transfer.

Specific measurements on Day 3 in the control group

Patients in both groups should have 2 things measured on day 3:

1. Static respiratory compliance should be measured (see page 22 for technique).
2. Specimens of blood and BAL should be collected (see below) – **after** static respiratory compliance has been measured. The BAL should be collected using the same technique as was used at baseline.

Transition from controlled to spontaneous mechanical ventilation in the control group

Pressure Support Ventilation (PSV) mode should be used to transition the patient from controlled to spontaneous mechanical ventilation. This mode should also be used if there are significant problems using controlled ventilation with patient-ventilator dysynchrony, difficulty in meeting aims, or because of strong clinician preference. The patients should be in either (1) SIMV Volume/Pressure Control mode with PSV or (2) PSV alone.

In PSV the goals of mechanical ventilation remain as follows:

- Tidal volume: ≤ 6 ml/kg PBW
- Plateau pressure [for controlled breaths]: ≤ 30 cmH_2O
- Total pressure [for spontaneous breaths] (ie. set inspiratory pressure + PEEP): ≤ 30 cmH_2O
- Breath rate: ≤ 35 breaths/minute
- pH: 7.30-7.45 (do not aim for a specific $PaCO_2$)
- SaO_2: 90-95% (if a PaO_2 is available, the aim for this is 60-80 mmHg).

Tidal volume targets should only be relaxed when the patient is clinically stable and receiving FiO_2 ≤ 0.5 and PEEP ≤ 10 cmH_2O. The inspiratory pressure for PSV can be adjusted down to a minimum of 5 cmH_2O (if tidal volume > 6 ml/kg PBW). If the tidal volume remains > 8 ml/kg PBW, there should be strong consideration to increase sedative drugs or to use a neuromuscular blocking drug so that controlled ventilation can replace (partially or completely) spontaneous mechanical ventilation. **Whilst PSV mode is being used, tidal volumes should be carefully monitored (including the use of mechanical ventilator alarms) with the aim that these remain approximately 6 ml/kg PBW.**

Management of severe hypoxaemia in the control group

If control group patients have a PaO_2 < 60 mmHg or a SaO_2 < 90% whilst receiving an FiO_2 and PEEP combination in any of the 5 columns at the right end of the FiO_2 and PEEP combination table (ie. FiO_2 ≥ 0.8 and PEEP ≥ 14), hypoxaemic rescue therapies should then be considered. These include prone positioning, inhaled nitric oxide, inhaled prostacyclin, high frequency oscillation and extracorporeal membrane oxygenation (ECMO), depending on the practice, availability, feasibility in the specific site and appropriateness.

No recruitment manoeuvres should be performed in control group patients unless there is no other feasible hypoxaemic rescue therapy able to be performed. Staircase recruitment manoeuvres should never be performed in the control group.

Resumption of the control group mechanical ventilation strategy should occur as soon as possible.

Weaning of mechanical ventilation in the control group

Please see the section below on “Weaning of mechanical ventilation for both groups”

Intervention group (PHARLAP) mechanical ventilation

Initial commencement of mechanical ventilation in the PHARLAP group

Mode: After randomisation, patients should be commenced in either Assist-Control (A/C) or Synchronised Intermittent Mandatory Ventilation (SIMV) using Pressure Control mode. All patients should be commenced in controlled rate ventilation, even if this requires additional sedation and/or neuromuscular blocking drugs. The PEEP level should remain at the pre-randomisation level.

The combined open lung procedure in the PHARLAP group (see Figure 1)

The initial procedure of the PHARLAP mechanical ventilation strategy should be to perform the combined open lung procedure which consists of (1) a staircase recruitment manoeuvre (SRM), followed by (2) a PEEP titration manoeuvre, and followed by (3) a brief recruitment manoeuvre (see Figure 1). This initial combined open lung procedure should be performed within 4 hours of randomisation.

This will then be followed by PHARLAP strategy mechanical ventilation.

The combined open lung procedure should be performed after assessment by an intensivist or registrar and when haemodynamic resuscitation is complete and circulatory parameters are stable. If vasopressors or inotropes are being used, a small transient increase prior to the combined open lung procedure will minimise any hypotension.

The **contraindications to a recruitment manoeuvre** (both the staircase and the brief manoeuvre) are:

- Mean systemic blood pressure < 60 mmHg despite attempts to augment BP with vasopressors/fluids.
- An active air leak through an intercostal catheter.
- Any radiographical evidence of pneumatoceles, subpleural cysts, or pericardial or mediastinal emphysema.
- Subcutaneous emphysema not related to trauma, surgical procedures, or ICU procedures.
- A supraventricular tachycardia associated with a mean systemic blood pressure < 70 mmHg, or any ventricular tachycardia.

If a patient has a contraindication to the combined open lung procedure, all other aspects of PHARLAP mechanical ventilation should be continued until the contraindication has resolved (when the combined open lung procedure should then be performed).

The combined open lung procedure should be performed as follows:

(1) Staircase recruitment manoeuvre (SRM):

The mechanical ventilator settings should be Pressure Control with an inspiratory pressure of 15 ± 3 cmH_2O depending on tidal volume achieved (pre-SRM tidal volume target 4-6 ml/kg PBW). The PEEP level should be left at the level it had been immediately prior to this procedure. The FiO_2 should be adjusted (usually by turning it down) until the SaO_2 is stable between 90-92%. This may take several (often 15-30 minutes). The high pressure alarm should be set to 65 cmH2O and the low tidal volume and minute ventilation alarms reduced to < 25% of the current settings.

Once the FiO_2 is stable (ie. no change for 3 minutes), the PEEP should be increased from the pre-randomisation baseline to 20 cmH_2O. In a stepwise fashion, this should be increased after 2 minutes to 30 cmH_2O (for 2 minutes) and then 40 cmH_2O (for 2 minutes), unless there is occurrence of (a) haemodynamic instability (defined as heart rate < 40 or > 140 bpm, ventricular tachycardia, or systolic blood pressure (SBP) < 80 mmHg), (b) marked oxygen desaturation (SaO_2 < 85%) or (c) new air leak through an intercostal catheter. The tidal volume should not be adjusted at each PEEP level, unless the tidal volume is > 6 ml/kg PBW.

The patient may cough or become restless at high PEEP levels. This may be due to expansion of collapsed lung and does not require the SRM to be discontinued. Transient reductions in tidal volume and minute ventilation are to be expected as the PEEP levels are increased. Sometimes the patient will require additional sedation.

If haemodynamic instability, marked oxygen desaturation or a new air leak occurs during the SRM, the SRM should be abandoned (with no further increases in PEEP occurring above the level where this occurred). If the

patient is considered to be inadequately haemodynamically resuscitated for their underlying condition, then it is preferable if vasopressor or fluid resuscitation should occur over the next 30-60 minutes, and then the combined open lung procedure be resumed. If the patient is considered to be adequately haemodynamically resuscitated, then fluid loading purely for the SRM should not be undertaken. The PEEP level one level below the PEEP level at which the SRM was abandoned should be determined as the **maximum tolerated PEEP** for this specific SRM and the PEEP titration manoeuvre should now occur (i.e. if marked desaturation occurs at 40 cmH_2O the maximum tolerated PEEP should then be determined as 30 cmH_2O). The maximum tolerated PEEP for the SRM will be determined daily and may be a different value on subsequent days.

If there is no occurrence of haemodynamic instability, marked oxygen desaturation or new air leak, the PEEP should be increased to the highest level of 40 cmH_2O. This should be determined as the maximum tolerated PEEP for this SRM.

(2) PEEP titration manoeuvre

After the final SRM step has been completed (or abandoned, as above), the PEEP should be immediately reduced to 25 cmH_2O. If, however, the SRM was abandoned at 20 cm H_2O, the PEEP titration should begin at 17.5 cm H_2O. The PEEP should be left at this first setting for 3 minutes, then decreased in steps by 2.5 cmH_2O for 3 minutes at each PEEP level to a minimum of 15 cmH_2O (i.e. from 25 to 22.5 to 20 to 17.5 to 15 cmH_2O) until the **de-recruitment PEEP** is reached. If the mechanical ventilator does not have 0.5 cmH_2O increments, round the PEEP up from 22.5 to 23 and 17.5 to 18 cmH_2O. The de-recruitment PEEP is defined as the PEEP level at which the SaO_2 first decreases by ≥ 2%. Once the de-recruitment PEEP has been reached, there should be no further reduction in PEEP, and the brief recruitment manoeuvre should now occur.

The PEEP should not be reduced below 15 cmH_2O if desaturation does not occur. In this situation, the PEEP should be left on 15 cmH_2O and no brief recruitment manoeuvre is required (ie. the combined open lung procedure has been completed).

(3) Brief recruitment manoeuvre

After this de-recruitment, a 2 minute brief recruitment manoeuvre should be performed (with the inspiratory pressure set at 15 ± 3 cmH_2O) using the PEEP level that was the maximum tolerated PEEP for the recently performed SRM. After this brief recruitment manoeuvre the PEEP should be returned to the level that is 2.5 cmH_2O above the de-recruitment PEEP. If there was no desaturation to determine the de-recruitment PEEP, the PEEP should be set at 15 cmH_2O and no brief recruitment manoeuvre is required. This final PEEP level should be considered the **daily optimal PEEP** (for the subsequent period - usually 24 hours) until a subsequent combined open lung procedure is performed.

Ventilation settings immediately after the combined open lung procedure

Plateau pressure, tidal volume and pH: Once the combined open lung procedure has been completed, the pressure control level should be reduced to achieve a total pressure (ie. inspiratory pressure + PEEP) ≤ 30 cmH_2O (preferably 25-28 cmH_2O) and a tidal volume of 4-6 ml/kg PBW. The tidal volume should be titrated down from 6 ml/kg towards 4 ml/kg if possible. The set breath rate should also be reduced aiming for a lowish pH (in the range of 7.15-7.30). The actual pH in an individual patient will depend on other factors (including level of sedation and other metabolic issues) and should be a clinical decision at the time.

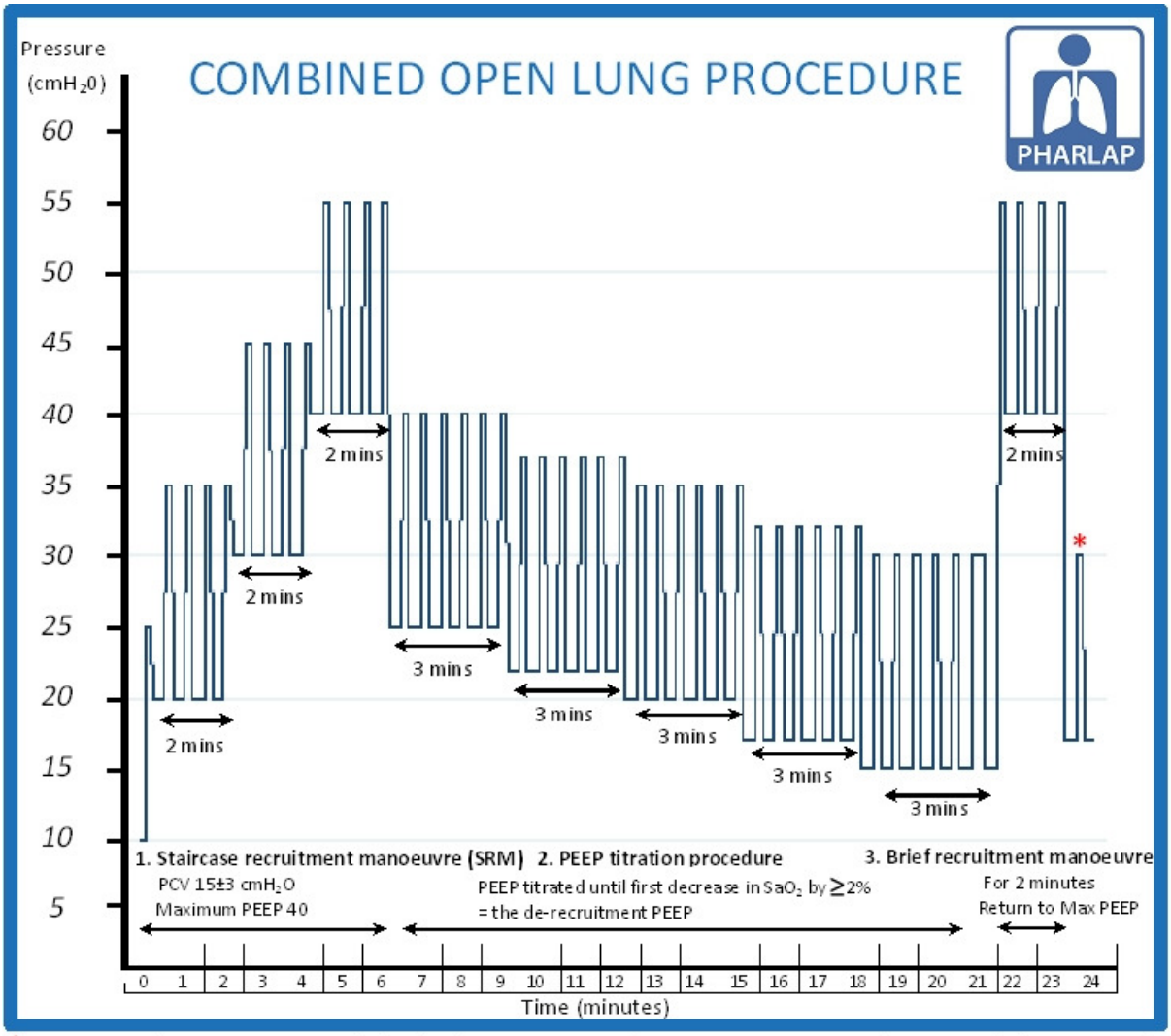
The mechanical ventilator alarms should be returned to their appropriate settings.

FiO_2 and PEEP: Immediately after the combined open lung procedure, the FiO_2 should be decreased until the SaO_2 is in the target range of 90-95%. One hour after the combined open lung procedure, the SaO_2 should be noted, and recorded on the bedside PHARLAP study ventilation sheet as the subsequent **daily precise SaO_2 target** for that day.

After this 1 hour time point, a SaO_2 ≤ 2% below this daily precise SaO_2 target should prompt strong consideration of re-recruitment using a brief recruitment manoeuvre (with or without an increase in FiO_2).

Over the subsequent hours, the FiO_2 should then be decreased (if SaO_2 > 95%) or increased (if SaO_2 ≤ 2% below this daily precise SaO_2 target), but the PEEP should not be weaned from the daily optimal PEEP setting. The only time the PEEP may be weaned is if there is significant haemodynamic instability, a new air leak through an intercostal catheter or if the SaO_2 is above the target range (≥ 95%) when the patient has been weaned to FiO_2 ≤ 0.4. The daily optimal PEEP will be determined again the next day as part of the daily combined open lung procedure.

The minimum PEEP in the PHARLAP group is 15 cmH_2O. It should only be reduced below 15 cmH_2O once the patient meets the readiness for weaning criteria (below).



* PHARLAP ventilation at 2.5 cmH_2O PEEP higher than de-recruitment PEEP (Minimum PEEP 15 cmH_2O until weaning and Pplat < 30 cmH_2O) e.g. if patient has ≥2% drop in SaO_2 at 17.5 cmH_2O PEEP then PHARLAP ventilation after brief recruitment manoeuvre at 20 cmH_2O PEEP

Neuromuscular blocking drugs: Neuromuscular blocking drugs should be used as judged appropriate by the treating clinician and their current unit policies.

Ongoing mechanical ventilation in the PHARLAP group

Goals: The goals of mechanical ventilation should always remain as follows:

- Tidal volume: 4-6 ml/kg PBW
- Breath rate: ≤ 35 breaths/minute
- Total pressure (ie. inspiratory pressure + PEEP): ≤ 30 cmH_2O (ideal range 25-28 cmH_2O)
- SaO_2 90-95% (if a PaO_2 is available, the aim for this is 60-80 mmHg). Within this range, re-recruitment using a brief recruitment manoeuvre is encouraged for reductions in SaO_2 of ≥ 2% below the daily precise SaO_2 target.

Permissive hypercapnia: The approach should be as follows:

- The tidal volume should be continue to be titrated downwards to achieve a tidal volume 4-6 ml/kg PBW and a plateau pressure < 30 cmH_2O (ideal range 25-28 cmH_2O). The set breath rate should also be reduced aiming for a lowish pH (in the range of 7.15-7.30).
- Hypercapnia and acidosis should be tolerated if pH ≥ 7.15.
- If pH < 7.15, the breath rate should be increased in steps of 4 to a maximum of 35 breaths/minute.
- If pH remains < 7.15 (after above), tidal volume should be increased by 1 ml/kg PBW at a time (but to a maximum total pressure [ie. inspiratory pressure + PEEP] of 35 cmH_2O.
- If pH remains < 7.15 (after above) and the patient is sedated as required, bicarbonate may then be considered. If the acidosis is predominantly metabolic, continuous renal replacement therapy may be required at this point.

If pH remains < 7.15 (after above) the tidal volume may be increased further but the PEEP should be reduced to maintain Pplat ≤ 35 cmH_2O.

Titrating the FiO_2 and PEEP: The PEEP should be left on the daily optimal PEEP determined by the most recent combined open lung procedure. The FiO_2 should be increased or decreased as required to maintain the SaO_2 aim. From day 6 onwards (i.e. after the 5 day period of performing combined open lung procedures has finished) the optimal PEEP should be set at 15 cmH_2O (or higher if clinically appropriate) unless the patient meets the readiness for weaning criteria.

Ongoing recruitment manoeuvres in the PHARLAP group

Combined open lung procedure: Subsequent combined open lung procedures (each being an SRM, a PEEP titration manoeuvre and a brief recruitment manoeuvre) should be performed daily for 5 days, unless the patient meets one of the following criteria to omit a combined open lung procedure:

(a) readiness for weaning criteria are met (see below),

(b) lack of improvement in static lung compliance criteria are met (on day 3, see below),

(c) there is a contraindication to a recruitment manoeuvre (see above), or

(d) it is the 6th day after enrolment (ie. 5 days of combined open lung procedures have occurred).

The initial combined open lung procedure should be performed within 4 hours of randomisation but subsequent combined open lung procedures should be performed during the daytime period (preferably during or soon after the morning or ICU ward round) such that one is performed on each consecutive chart day (unless the patient meets one of these criteria to omit a combined open lung procedure).

The daily combined open lung procedure should be performed as it was on the initial occasion, however each day there may be a different maximum tolerated PEEP, a different de-recruitment PEEP and a different daily optimal PEEP level determined. There should also be a different precise SaO_2 target determined 1 hour after the combined open lung procedure and which should be the new daily precise SaO_2 target. Each of these will then remain until a subsequent combined open lung procedure is performed (usually 24 hours later).

Neither the combined open lung procedure nor independently performed SRMs should be performed at times other than this daily morning intervention.

The **lack of improvement in static lung compliance** definition will be met if the static lung compliance after the staircase recruitment manoeuvre on day 3 is lower than the static lung compliance assessed prior to the performance of the initial (day 1) combined open lung procedure. Any patient who meets this criterion will have no further combined open lung procedures or brief recruitment manoeuvres and should have the PEEP set on 15 cmH_2O (or higher if clinically appropriate) unless the patient meets the readiness for weaning criteria.

No combined open lung procedures or brief recruitment manoeuvres should be performed after day 5. If the patient has not met readiness for weaning criteria, the optimal PEEP should be set at 15 cmH_2O (or higher if clinically appropriate) unless the patient meets the readiness for weaning criteria.

Desaturation: We recommend patients receive a chest x-ray for significant persistent desaturation to rule out barotrauma before a brief recruitment manoeuvre or further combined open lung procedures are performed.

Brief recruitment manoeuvre: A brief recruitment manoeuvre should be performed independently (ie. without an SRM and individual PEEP titration) if an oxygen desaturation occurs (≥ 2% below the daily precise SaO_2 target). This may occur without a clear precipitating event or may occur as a result of (a) an intervention (eg. suction, cuff deflation, body position change, coughing episode, waking) or a mechanical ventilator disconnection. Disconnections include inadvertent extubations (followed by reintubation), and any inadvertent disconnections of the endotracheal tube or tracheostomy tube from the ventilator circuit however brief these may be. Disconnections for tracheostomy care and changes of in-line suction catheters should be followed by a brief recruitment manoeuvre. Disconnections occurring due to patient transfer for a procedure (eg. radiology department, operating theatre) or to move the patient to another ICU bedspace should be followed by a brief recruitment manoeuvre only after the patient has been reconnected to the ventilator back in the ICU. For example, a transfer to the radiology department may have several associated disconnections (from the ICU ventilator, from a transfer ventilator, from a ventilator in the radiology suite, from the transfer ventilator again). These should be considered together as one disconnection, and the brief recruitment manoeuvre performed only upon return to the ICU with reconnection to the ICU ventilator. If an episode of in-line suctioning is performed without a clear disconnection, a brief recruitment manoeuvre is not required.

Similarly to the combined open lung procedure, independently performed brief recruitment manoeuvres should not be performed if:

(a) readiness for weaning criteria are met (see below),

(b) lack of improvement in static lung compliance criteria are met (on day 3, see below),

(c) there is a contraindication to a recruitment manoeuvre (see above), or

(d) it is the 6th day after enrolment (ie. 5 days of combined open lung procedures have occurred).

If an oxygen desaturation (≥ 2% below the daily precise SaO_2 target) occurs with a clear precipitating event (i.e. intervention or ventilator disconnection), the brief recruitment manoeuvre should be performed as follows:

- The PEEP should be increased to the maximum tolerated PEEP determined during the most recently performed SRM, left at that level for 2 minutes, and then immediately returned to the daily optimal PEEP determined by that same SRM.

If an oxygen desaturation (≥ 2% below the daily precise SaO_2 target) occurs with no clear precipitating event (ie. potentially a deterioration in lung function), the brief recruitment manoeuvre should be performed as follows:

- The PEEP should be increased to the maximum tolerated PEEP determined during the most recently performed SRM, left at that level for 2 minutes, and then immediately returned to 2.5 cmH_2O (rounded up by 0.5 if the ventilator does not use 0.5 cmH_2O settings) higher than the previous daily optimal PEEP set during that SRM.
- This new PEEP level should be considered the new daily optimal PEEP level for the subsequent part of that day until the next SRM is performed. The FiO_2 should then be decreased as required to maintain the SaO_2 aim.
- The PEEP should not be set higher than 25 cmH_2O at any time during the study (with the exception of the staircase recruitment manoeuvre).

Brief recruitment manoeuvres should not be repeated more frequently than 2 hourly and not more than a maximum of 4 manoeuvres per 24 hours.

Ventilation during patient transfers: Mechanical ventilation should continue to adhere to this PHARLAP group strategy during patient transfers (to diagnostic or therapeutic procedures outside the ICU) where possible. However if the patient receives mechanical ventilation using either a manual (hand-bagging) circuit or a transport ventilator that is not practically able to deliver the PHARLAP group mechanical ventilation settings, patients may be ventilated using alternative means whilst away from the ICU. Resumption of PHARLAP group mechanical ventilation (including performance of a brief recruitment manoeuvre if indicated)

should occur as soon as possible after the transfer. A brief recruitment manoeuvre will usually be required (see above on this page).

Specific measurements on Day 3 in the PHARLAP group

Patients in both groups should have 2 things measured on day 3:

1. Static respiratory compliance should be measured (see page 22 for technique).
2. Specimens of blood and BAL should be collected (see below) – **after** static respiratory compliance has been measured. The BAL should be collected using the same technique as was used at baseline.

If the patient has been assigned to the PHARLAP group, this procedure should now be followed as soon as possible by a brief recruitment manoeuvre (see below).

Transition from controlled to spontaneous mechanical ventilation in the PHARLAP group

Pressure Support Ventilation (PSV) mode should be used to transition the patient from controlled to spontaneous mechanical ventilation. This mode should also be used if there are significant problems using controlled ventilation with patient-ventilator dysynchrony, difficulty in meeting aims, or because of strong clinician preference. The patients should be in either (1) Pressure Control mode with PSV or (2) PSV alone.

In PSV the goals of mechanical ventilation remain as follows:

- Tidal volume: 4-6 ml/kg PBW
- Plateau pressure [for controlled breaths]: ≤ 30 cmH_2O (ideal range 25-28 cmH_2O)
- Total pressure [for spontaneous breaths] (ie. inspiratory pressure + PEEP): ≤ 30 cmH_2O (ideal range 25-28 cmH_2O
- Breath rate: ≤ 35 breaths/minute
- pH: > 7.15 (do not aim for a specific $PaCO_2$)
- SaO_2: 90-95% (if a PaO_2 is available, the aim for this is 60-80 mmHg).

Tidal volume targets should only be relaxed when the patient is clinically stable and receiving FiO_2 ≤ 0.5. The inspiratory pressure for PSV can be adjusted down to a minimum of 5 cmH_2O (if tidal volume > 6 ml/kg PBW). If the tidal volume remains > 8 ml/kg PBW, there should be strong consideration to increase sedative drugs or to use a neuromuscular blocking drug so that controlled ventilation can replace (partially or completely) spontaneous mechanical ventilation. **Whilst PSV mode is being used, tidal volumes should be carefully monitored (including the use of mechanical ventilator alarms) with the aim that these remain approximately 6 ml/kg PBW.**

As lung recovery occurs, the FiO_2 should be reduced to maintain the SaO_2 in the target range. **There should be no reductions in PEEP until the SaO_2 ≥ 90% whilst receiving FiO_2 ≤ 0.4 for 4 continuous hours.**

Management of severe hypoxaemia in the PHARLAP group

If PHARLAP group patients have a PaO_2 < 60 mmHg or a SaO_2 < 90% whilst receiving FiO_2 ≥ 0.8 and (a) this does not improve with a brief recruitment manoeuvre (see procedure above), or (b) a brief recruitment manoeuvre is not indicated based on one of the criteria listed above, hypoxaemic rescue therapies should then be considered. These include prone positioning, inhaled nitric oxide, inhaled prostacyclin, high frequency oscillation, and extracorporeal membrane oxygenation (ECMO), depending on the practice, availability and feasibility in the specific site and appropriateness.

In PHARLAP group patients, no staircase recruitment manoeuvres should be performed other than the planned daily combined open lung procedure up until day 5. No brief recruitment manoeuvres should be performed in PHARLAP group patients after day 5 unless there is no other feasible hypoxaemic rescue therapy able to be performed.

Resumption of PHARLAP group mechanical ventilation strategy should occur as soon as possible.

Weaning of mechanical ventilation in the PHARLAP group

Please see the section below on “Weaning of mechanical ventilation for both groups”

Weaning of mechanical ventilation in both groups

Daily screening of patients in both groups

Patients should be screened at least once per day for readiness to wean.

Readiness for weaning

Patients in both groups will be deemed to have met **readiness for weaning** criteria when for the first time the patient has (1) $SaO_2 \geq 90\%$ whilst receiving $FiO_2 \leq 0.4$ for ≥ 6 continuous hours, and (2) is considered otherwise clinically stable.

- If the patient does not meet readiness for weaning criteria, mechanical ventilation aims should remain as recommended above for the patient's group assignment.
- Once a patient meets readiness for weaning criteria the first time, no further recruitment manoeuvres (combined open lung procedure or brief recruitment manoeuvres) should be performed in the PHARLAP group. If possible, the patient should have the PEEP reduced by 2.5 cmH_2O (rounded up by 0.5 if the ventilator does not use 0.5 cmH_2O settings) at a time. Subsequent reductions in PEEP should be no sooner than 4 hours after the previous reduction. All other mechanical ventilation aims should remain as recommended above for the patient's group assignment.
- If the patient's respiratory function deteriorates after weaning criteria has been met the following can occur:

  - **Control patients:**
    - Continue using control group ventilation strategy and reassess readiness for weaning the next day
  - **PHARLAP treatment patients**:
    - If it is day 2 to 5 and the Cstat did improve then a COLP should be performed and the PEEP titrated as per the PHARLAP group protocol.
    - If it is after day 5 or the Cstat did not improve on day 3 change the PEEP to the default level 15cmH_20 (may be higher if deemed clinically appropriate) and titrate the FiO_2 to maintain oxygen saturation ≥ 90% and reassess the readiness for weaning the next day.

Readiness for unassisted breathing trial

Patients in both groups will be deemed to have met **readiness for an unassisted breathing trial** when the patient meets all of (1) $SaO_2 \geq 90\%$ whilst receiving $FiO_2 \leq 0.4$ and PEEP ≤ 10 cmH_2O for ≥ 6 continuous hours, (2) has intact airway reflexes and low amounts of sputum, (3) has a reasonable level of consciousness whilst receiving low doses of or no sedative infusions, and (4) is considered otherwise clinically stable and mechanical ventilator liberation is considered appropriate (e.g. there is no imminent procedure requiring ongoing mechanical ventilation).

- If the patient does not meet readiness for an unassisted breathing trial, mechanical ventilation aims should remain as recommended above for the patient's group assignment, including ongoing progressive weaning of PEEP as possible in the PHARLAP group.
- Once a patient meets readiness for an unassisted breathing trial, a period of unassisted breathing should commence on the same day. Unassisted breathing is allowing the patient to breathe spontaneously on any one of a T-Tube circuit, a tracheostomy mask/hood/shield or a mechanical ventilator circuit using CPAP 5 cmH_2O with minimal support (ie. PSV ≤ 10 cmH_2O). The FiO_2 should be ≤ 0.5.

Readiness for mechanical ventilator liberation

Patients in both groups will be deemed to have met **readiness for mechanical ventilator liberation** criteria if after at least 30 minutes of an unassisted breathing trial, the patient meets all of (1) breath rate < 35 breaths/minute, (2) $SaO_2 > 90\%$ whilst receiving $FiO_2 \leq 0.5$, (3) systolic blood pressure > 90 and < 180 mmHg, (4) heart rate either (a) < 140 beats/minute or (b) not increased by > 20% since the beginning of the unassisted

breathing period, and (5) is considered otherwise clinically stable and mechanical ventilator liberation is not considered inappropriate.

- If the patient does not meet readiness for mechanical ventilator liberation criteria, mechanical ventilation aims should remain as recommended above for their group assignment until the next day, when readiness for weaning should be reassessed. If the unassisted breathing trial led to desaturation this may require an increase in FiO_2 or PEEP. In the PHARLAP group no further recruitment manoeuvres should be performed unless severe desaturation occurs (requiring $FiO_2 \geq 0.8$). In this situation a brief recruitment manoeuvre should be considered.
- Once a patient meets readiness for mechanical ventilator liberation criteria, they should, on the same day, be either (1) extubated or (2) placed on a tracheostomy mask/hood/shield for an indefinite period. Intermittent periods of mechanical ventilation and tracheostomy mask/hood/shield breathing should only occur once it has been deemed clinically necessary by the patient meeting criteria for consideration for further invasive mechanical ventilation.

Consideration for further invasive mechanical ventilation

Patients in both groups will be deemed to have met **consideration for further invasive mechanical ventilation** if they develop any of (1) hypoxaemia ($SaO_2 \leq 90\%$ or $PaO_2 < 60$ mmHg) whilst receiving $FiO_2 \geq 0.5$, (2) respiratory distress (judged clinically), (3) tachypnoea (breath rate > 35 breaths/minute), (4) inability to clear airway secretions (judged clinically), (5) upper airway obstruction, or (6) decrease in consciousness (judged clinically).

- If the patient does not meet consideration for further invasive mechanical ventilation, they should continue indefinitely to receive no invasive mechanical ventilatory support.
- Once a patient meets consideration for further invasive mechanical ventilation after having been extubated, reintubation should be considered. Non-invasive ventilation is not recommended after recent extubation. If the patient is reintubated, they should continue to receive mechanical ventilation as recommended above for their group assignment. In most cases, this should be a brief period of controlled ventilation, followed by transition to spontaneous mechanical ventilation. If the patient is in the PHARLAP group, no further combined open lung procedures are mandated, although a brief recruitment manoeuvre should be considered. The subsequent mechanical ventilator disconnection plan should be made with the aim of complete mechanical ventilator liberation as soon as possible.
- Once a patient meets consideration for further invasive mechanical ventilation after having been placed on a tracheostomy mask/hood/shield, reconnection to the mechanical ventilator should be considered. If the patient has invasive mechanical ventilator reconnection, they should continue to receive mechanical ventilation as recommended above for their group assignment. In most cases, this should be spontaneous mechanical ventilation in pressure support mode. If the patient is in the PHARLAP group, no further combined open lung procedures are mandated, although a brief recruitment manoeuvre should be considered. The subsequent mechanical ventilator disconnection plan should be made with the aim of complete mechanical ventilator liberation as soon as possible.

Fluid management in both groups

The patient should have the aim of a fluid balance that best suits their clinical state during the first day of the study.

The general aim from day 2 is to ignore the day 1 fluid balance and attempt to achieve a cumulative neutral fluid balance thereafter, unless there is a clear indication for a positive or negative fluid balance[50].

If there is an unplanned positive fluid balance it should be corrected by fluid restriction (including consideration of concentrated enteral nutrition formulations and diuretics).

Significant peripheral oedema should be corrected with fluid restriction and diuretics, unless contra-indicated.

Careful monitoring of renal function and other indices of organ perfusion should occur.

If haemodynamic instability occurs during the combined open lung procedure (mainly during the SRM), vasopressors should be considered initially. Intravenous fluid boluses should be administered if vasopressor requirements increase rapidly.

Use of corticosteroids in both groups

Steroids should not be used specifically for ARDS after day 7[51].

Other interventions in both groups

All other interventions will not be standardised. Given the possibility of confounding by different utilisation rates of various interventions between groups, data will be collected on haemodynamics (daily central venous pressure, blood pressure and heart rate), fluid balance, pulmonary artery catheter usage, intravenous bicarbonate usage, renal replacement therapy usage, neuromuscular blocking drug usage, corticosteroid usage and hypoxaemic rescue therapy usage.

Discontinuation of treatment

Patients in both groups will receive their assigned ventilator strategy until any of the following occur:

1. The patient is no longer receiving mechanical ventilation
2. The patient dies or is discharged from the Intensive Care Unit
3. The patient or surrogate decision-maker withdraws informed consent.

Table of events

Please see Appendix 3

Laboratory sampling

Blood (10 ml centrifuged to isolate plasma) and BAL (10 ml taken using the technique described above) samples will be collected and stored -80^{o}C at each site at baseline and day 3. Samples will be shipped in 2 batches to a central processing laboratory (Flinders Medical Centre) for quantification of IL-6, IL-8 and protein concentration by blinded laboratory scientists.

ETHICAL CONSIDERATIONS

Guiding principles

This study is to be performed in accordance with the ethical principles of the Declaration of Helsinki (June 1964 and amended 1975, 1983, 1989, 1996, 2000, 2008 and Note of Clarification 2002 and 2004), ICH GCP Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with Therapeutic Goods Administration comments, NHMRC National Statement on Ethical Conduct in Research Involving Humans (March 2007); the New Zealand Interim Good Clinical Research Practice Guidelines (Volume 2 1998 and Volume 3 2000) and ICH GCP Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95).

Ethical issues of the study

The two major ethical considerations in this study are:

- The enrolment of participants who are unable to provide their own informed consent
- Confidentiality of patient data outside the participating institution

Informed consent

The NHMRC National Statement on the Ethical Conduct of Research in Humans (March 2007) acknowledges in Chapter 4.4 that in research studies involving patients who are heavily dependent on medical care, such as the patients in this study, it is necessary to assess the efficacy and safety of interventions used in their treatment. Patients who are sedated and mechanically ventilated will not be able to provide informed consent.

Consent will be obtained from the participant's parent or guardian, a legal surrogate or an organisation authorised by law (NS 4.4.10). The criteria of who may give consent for a patient to take part in medical research (and the term with which they may be described) varies at participating sites. For the purposes of this protocol, the descriptor "legal surrogate" describes the person who is legally allowed to give consent for the patient.

The legal surrogate will be invited to consider the patient's consent for participation after a verbal presentation, followed by reading of the "person responsible" information and consent form. There will be sufficient time provided for thought, reflection, questions and consultation with others. If the legal surrogate provides consent for the patient to participate in the study, they will be asked to sign the consent form.

In cases where the legal surrogate cannot attend the hospital to sign the consent form within the time constraints of the study, consent for patient participation in the study may be obtained over the telephone in accordance with local Human Research Ethics Committee guidelines. The telephone conversation will be documented in the patient's medical record. As soon as the legal surrogate is able to attend the hospital they will be asked to sign a consent form and note that telephone consent was already provided.

The legal surrogate will be able to withdraw their consent for the patient to participate in the study at any time without any reduction in the quality of care, and if they choose to withdraw the patient, permission will be asked to use the data collected up until that time.

Patients who recover sufficiently to provide their own informed consent will be asked to consent to continue in the study or offered the chance to withdraw (as per NS 4.4.14). If the patient chooses to withdraw from the study, they will be asked for permission to use their data up to the time of withdrawal.

All interaction between research staff and potential or actual participants and their legal surrogate will take into consideration the stress or emotional factors associated with critical illness and ensure that the dependency of potential participants and their relatives on medical personnel providing treatment does not compromise the freedom of decision making to participate (as per NS 4.4.11).

Confidentiality of patient data

Patients will be randomised via a secure website and will be allocated a unique study number. The site research coordinator will compile an enrolment log including the patient's name, date of birth, hospital identification number, unique study number and date and time of randomisation. Other collected data (using a case report form and entered on the study website) will be identified by the unique study number, but will not

contain this more identifying personal information. The enrolment log will be kept separately to the case report form and the study website, so that the personal information is only kept at the specific enrolling site. Contact details of the patient and their family will be collected, including name, address and telephone numbers, to allow follow-up assessments to occur. The contact details will be forwarded to the coordinating centre, as follow-up assessments (phone interviews) will be performed by the coordinating centre (ANZIC-RC) to ensure consistency and accuracy. All data collected in the follow up assessments will be identified by the unique study number. The follow up contact details will be kept separately to the case report form and the study website. Study data will be entered into a password protected website and database managed by the CIDMU (Monash University). None of the personal information will be entered into the database. The contact details and study data will be kept in a locked office at both the study site and the coordinating centre.

Ethics committee approval

Each participating site will submit this protocol and any other relevant study documentation to the responsible local Human Research Ethics Committee (or equivalent). Approval of the protocol, plans for obtaining informed consent, and study-related documents will be obtained prior to the start of the study at each site.

The site principal investigator will be responsible to ensure that all conditions for approval of the study are met and that amendments to the protocol or serious adverse events are also reported to the Human Research Ethics Committee (HREC, or equivalent) as required.

This protocol will also be submitted to the Guardianship Board or similar where this is necessary for legal surrogates to provide informed consent for patient participation. The site principal investigator will be responsible to obtain such approval from the relevant body prior to obtaining legal surrogate consent.

DATA MANAGEMENT

Data collection methods

All study-related data will be collected by trained staff at each study site using a paper source document (case report form) developed by the coordinating centre. Data will then be entered into an internet-based database designed by the CIDMU. Data queries will be automatically generated as they are entered into this database.

Enrolled patients will be followed up to death or 6 months post-enrolment. Data collection will be restricted primarily to those variables necessary to define clinical patient characteristics including: baseline demographics, primary diagnoses, physiological parameters, diagnostic interventions, therapeutic interventions and documentation of deaths, other serious adverse events, and patient outcomes.

Patients and/or their legal surrogate will be asked to provide three possible points of contact (home and close family contact details) to the research staff prior to discharge. Full protocol data will be collected in all patients including those where the study is discontinued prior to the end of the study period. Patients (or a surrogate – generally a close family member) who are alive at 6 months after enrolment will be asked to complete a questionnaire via post or telephone by a trained follow-up assessor from the coordinating centre. This follow-up assessor will use a standardized structured telephone questionnaire[52] to measure the QOL assessments EQ-5D[53] and SF- 36v2[54,55].

Data variables collected

- Demographic data
- Height
- Weight
- Admission diagnosis
- Cause of ARDS
- Classification of ARDS as diffuse or focal (by an independent radiologist)
- PaO_2/FiO_2 ratio at enrolment
- Barotrauma
- Mode of ventilation
- Ventilation parameters
- ABG results
- Vital signs
- SOFA scores
- Daily fluid balance
- Rescue therapy details
- Co-interventions
- Open lung procedure details
- Ventilation weaning
- Adverse events
- Serious adverse events
- Protocol deviations
- Outcomes – duration of ventilation, length of stay, survival, discharge destination

- Long term outcomes (at 6 months) – SF36, EQ5D, cost-effectiveness analysis

Data management

Data management will be performed by the CIDMU at the Department of Epidemiology and Preventive Medicine, Monash University.

Monitoring

The study will be monitored by a representative of the coordinating centre. Prior to study commencement, a start-up teleconference or visit will be conducted at each site. Monitoring of the data collection and protocol adherence will occur after study completion for the first intervention and control patient at each site.

The database will be developed to routinely report queries and protocol violations. Additional queries will be generated by the Project Manager following regular reviews of the data. Additional on-site monitoring will also be performed if the routine reviews indicate any significant issues at individual sites. Email and telephone communication will supplement site visits.

A monitoring report will be prepared following each visit and reviewed by the management committee. A follow up letter will be sent to the principal investigator and research coordinator at the site and will be filed in the site investigator file.

Medical records, any other relevant source documents and the site investigator files will be required to be made available to the coordinating centre representative for these monitoring visits during the course of the study and at the completion of the study as needed.

The aims of monitoring visits are to:

a) Check data accuracy by performing source data verification of the electronic case report form against the original source documents

b) Check for protocol deviations to report these to the Management Committee as necessary

c) Review primary and secondary outcome data collected for each patient

d) Confirm the informed consent procedures approved by the site's HREC have been followed and view each original signed consent form

e) Check data security and access

f) Review all serious adverse events (SAEs) to allow follow up of all reported SAEs

g) Review investigator site files for completeness and accuracy

h) Assist the study staff with any queries or problems they may have in relation to the study

Protocol deviations

A protocol deviation is an unanticipated or unintentional departure from the expected conduct of an approved study that is not consistent with the current research protocol or consent document. A protocol deviation may be an omission, addition or change in any procedure described in the protocol.

Given that investigators are responsible for patient safety and care, they may implement a deviation from, or a change of, the protocol to deal with an immediate hazard to trial patients without prior HREC approval. The implemented deviation or change must be reported in a protocol deviation form. The deviation must be reported by the principal investigator using the case report form so that it can be reported to the coordinating centre and the HREC (if applicable).

STATISTICAL CONSIDERATIONS

Power calculations and sample size

Based on data from the PHARLAP pilot study, with 282 subjects this study will have an 80% power to detect a difference equal to 33% of a standard deviation (equal to3VFD's) with a two sided p-value of 0.05. To account for likely occurrence that VFD will not follow a normal distribution, the sample size has been inflated by 15% to 324 in accordance with Lehmann[56]. Allowing for up to a 5% rate for withdrawal or loss to long term follow up, 340 patients will be enrolled.

Statistical and analytical plan

Independent senior statisticians at Monash University will perform data analysis. Baseline and outcome variables will be compared using Chi-square tests for categorical variables, Student's t-test for normally distributed continuous variables and Wilcoxon rank-sum tests for non-normally distributed continuous variables. Duration of ventilation will be analysed using Cox-Proportional Hazards regression with deceased patients censored at death, allowing for results to be reported using Kaplan Meier curves. Furthermore, duration of ventilation will be stratified into survivors and non-survivors. If as expected, the duration of ventilation in each strata is well approximated by a log-normal distribution, this will enable log-transformed duration of ventilation to be analysed using parametric analysis (student t-tests) and reported as a ratio (95%CI). If normality cannot be achieved then the data would subsequently be analysed non-parametrically. Should any baseline imbalances be found to exist between groups, additional sensitivity analysis will be performed using Cox Proportional Hazards regression adjusting for imbalanced covariates. All analyses will be intention-to-treat. A complete statistical analysis plan will be finalised prior to study completion.

Interim analysis

One midpoint interim analysis (after primary outcome data is available for 170 patients) will be performed to assess accumulated safety data. This will be reported to the Data Safety Monitoring Committee, but will not be made available to the Management Committee or to study sites.

Subgroup analyses

We plan to compare study outcomes in the following pre-specified subgroups:

(a) Patients with severe ARDS (PaO_2/FiO_2 < 100) versus patients with moderate ARDS (PaO_2/FiO_2 100-200 mmHg) at enrolment.

(b) Patients with diffuse ARDS versus patients with focal ARDS at enrolment (determined by independent radiologists).

(c) Patients who are responders to the open lung strategy versus patients who are non-responders (defined as meeting lack of improvement in static lung compliance definition).

SAFETY OF SUBJECTS

Data Safety Monitoring Committee

An independent Data Safety Monitoring Committee, comprising experts in clinical trials, biostatistics and intensive care will be established. The committee will be responsible for monitoring mortality related to serious adverse events, serious adverse events and reviewing the interim safety analysis.

Adverse events

Adverse events are defined as any untoward medical occurrence in a patient or clinical investigation subject administered an investigational intervention and does not necessarily have to have a causal relationship with this intervention (adapted from the Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95 July 2000).

It is recognised that the patient population with critical illness and ARDS will experience a number of common aberrations in laboratory values, signs and symptoms due to the severity of the underlying illness and the impact of standard therapies. These will not necessarily constitute an adverse event unless they require significant intervention or are considered to be of concern in the investigator's clinical judgement.

In all cases, the condition or disease underlying the symptom, sign or laboratory value should be reported e.g. renal failure rather than hyperkalaemia, and agitation rather than self-extubation.

Serious adverse events

Serious Adverse Events (SAE) are defined in accordance with the Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95) (July 2000) as any one of the following untoward medical occurrences:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event which may require intervention to prevent one of the previously listed outcomes

In this study all SAEs will be reported if they possibly, probably or causally are related to study enrolment. However, consistent with the advice of Cook et al, adverse events already defined and reported as study outcomes (mortality) will not be labelled and reported a second time as serious adverse events.

Reporting of SAEs

Separate case report forms will be developed to record adverse events and serious adverse events.

SAEs which occur from the time of enrolment until day 90 follow-up will be reported to the coordinating centre via the internet-based SAE form. SAEs should be reported to the coordinating centre within 24 hours of study staff becoming aware of the event.

Minimum information to report will include:

- Patient initials and study number
- Nature of the event
- Commencement and cessation of the event

- An investigator's opinion of the relationship between study involvement and the event (unrelated, possibly, probably or definitely related).
- Whether treatment was required for the event and what treatment was administered.

Website address: https://pharlap.org.au

Telephone Numbers:

ANZIC-RC: +61 3 99030280

ANZIC-RC: +61 409367132

Chief investigator: + 61 419770132

SAEs must be reported using the study website. The event and report may be discussed with the coordinating centre staff or chief investigator if necessary. Coordinating centre staff will be responsible for following-up SAEs to ensure all details are available. The site principal investigator is responsible for inform the relevant HREC of all SAEs which occur at their site, in accordance with local requirements.

FUNDING

The PHARLAP study is funded by project grants from the National Health and Medical Research Council (NHMRC) (Project grant no APP1021203), the Alfred Hospital, and the Health Research Council of New Zealand. The ANZIC-RC will supply infrastructure and administrative support.

PUBLICATION

The study will be conducted in the name of the PHARLAP investigators, the ANZIC-RC and the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG). The study has been endorsed by the ANZICS CTG. The principal publication from the study will be authored as "The PHARLAP Study Investigators for the ANZICS CTG". This will be on behalf of the writing committee and all PHARLAP Investigators with full credit being assigned to all collaborating investigators, research coordinators and institutions. Where an individual's name is required for publication it will be that of the writing committee, with the chair of the writing committee listed first and subsequent authors listed alphabetically.

Funding bodies will be acknowledged in the publication.

Other manuscripts and sub-studies may be authored differently but these must follow the conditions of ANZICS CTG endorsement and be approved by the PHARLAP MC. This may lead to manuscripts authored by a list of individual authors on behalf of the PHARLAP Study Investigators for the ANZICS CTG.

PROJECT TIMELINE

Timeframe Indicator	Milestone
January 2011	ANZICS CTG endorsement
April 2011	NHMRC funding application submitted
August 2011	Alfred Hospital funding application successful
October 2011	NHMRC funding application successful
November 2011	Commencement of study organisation
September 2012	Protocol and Case Report Forms finalised
October 2012	Participating sites finalised
August-February 2013	Participating sites HREC applications
August 2012-April 2013	Participating sites HREC approval
October 2012	Sequential site start up and education visits
October 2012	Study recruitment commences
August 2015	Interim analysis
May 2016	Patient recruitment completed
November 2016	6 month follow up of all patients completed
December 2016	Query resolution and final data completion
January 2017	Database lock
February 2017	Primary analysis completed
March 2017	Results presentation and manuscript completion

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APPENDIX 1: PREDICTED BODY WEIGHT (PBW) CALCULATION

• **Male:** PBW (in kg) = 50 + 0.91 [height (cm) – 152.4]

• **Female:** PBW (in kg) = 45.5 + 0.91 [height (cm) – 152.4]

Ref: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. The New England Journal of Medicine 2000;342:1301-8.

Use true height if this has been measured accurately in the last few days. If not, use estimated height from measurement of the demi-arm span.

The demi-arm span should be measured using the right arm (preferably) and by measuring between the base of the fingers where the middle and ring fingers meet to the sternal notch. The patients' right arm should be extended until it is horizontal with the shoulder. Ensure the wrist is straight. The patients' arm may need to be supported.

The estimated height can then be calculated from the measured demi-arm span as follows:

• **Male:** Height (in cm) = (1.40 X demi-arm span (cm)) + 57.8

• **Female:** Height (in cm) = (1.35 X demi-arm span (cm)) + 60.1

APPENDIX 2: BRONCHOALVEOLAR LAVAGE (BAL) FLUID COLLECTION

Non-bronchoscopic method:

1. Pre-oxygenate the patient by increasing the FiO_2 to 1.0 for 2 minutes. The PEEP should be left on the current setting.

2. Draw up 60 ml of 0.9% saline in appropriate syringes (usually three 20 ml syringes). Prepare a clean environment as per the usual site practice for similar interventions.

3. Connect one of the 0.9% saline syringes to the upper port on the 3 way tap and point the off arrow to the other port. Ensure the blue locking device is open.

4. Introduce the BAL catheter by forwarding the catheter through connector B so that the catheter tip protrudes through the connector before connecting to the endotracheal tube.

5. Disconnect the in-line suction and ventilator and attach connector B to the endotracheal tube – the catheter should be 2 cm into the endotracheal tube. Reconnect the ventilator tubing to connector B.

6. Advance the catheter until the numbers on the catheter match the numbers on the endotracheal tube. At this point the catheter is located exactly at the distal point of the endotracheal tube.

7. Ensure the white oxygen port on the catheter is orientated to the right. This means that the internal catheter will be angled towards the right main bronchus.

8. Forward the entire catheter another 5 cm and check that the white oxygen port remains orientated to the right side.

9. Flush the catheter with 5 ml 0.9% saline. Lock the blue locking device.

10. Gently advance the inner catheter until a spongy resistance is noted (ie. the catheter is appropriately wedged in a distal bronchus).

11. Inject the first syringe of 0.9% saline, followed by 5 ml air. With the same syringe, gently hand aspirate the BAL, then do the same with subsequent syringes via the 3 way port until a minimum volume of 10ml. is obtained.

12. Withdraw the inner suction catheter until the solid black mark is outside the connector to the endotracheal tube. Unlock the blue locking device. Withdraw the entire catheter. Reconnect the in-line suction catheter and the original connectors.

13. Combine the collected BAL fluid from each syringe into a sterile container and label this as a BAL for the PHARLAP study.

14. If the patient has been assigned to the PHARLAP group, this procedure should now be followed as soon as possible by a combined open lung procedure (see page 26) if it is day 1 or a BRM if it is day 3.

Bronchoscopic method:

1. Pre-oxygenate the patient by increasing the FiO_2 to 1.0 for 2 minutes. The PEEP should be left on the current setting.

2. Draw up 60 ml of 0.9% saline in appropriate syringes (usually three 20 ml syringes). Prepare a clean environment as per the usual site practice for similar interventions.

3. Wedge the bronchoscope in the appropriate bronchus.

4. Inject the first syringe of 0.9% saline, followed by 5 ml air. With the same syringe, gently hand aspirate the BAL, then do the same with subsequent syringes until a minimum volume of 10 ml is obtained.

5. Combine the collected BAL fluid from each syringe into a sterile container and label this as a BAL for the PHARLAP study.

6. If the patient has been assigned to the PHARLAP group, this procedure should now be followed as soon as possible by a combined open lung procedure (see page 26) if it is day 1 or a BRM if it is day 3.

APPENDIX 3: SCHEDULE OF EVENTS

Assessments/ Procedures	Pre Randomisation/ Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6 till liberation of mechanical ventilation	ICU discharge	Hospital discharge	Follow-up 28 days	Follow-up 90 days	Follow-up 6 months
Inclusion & Exclusion criteria	X											
Consent	X											
Randomisation	X											
Demographic data	X											
Height & weight measurement	X											
CXR	X											
Download CXR image	X											
Apache II score	X											
Apache III diagnosis	X											
SOFA score	X	X	X	X	X	X	X					
Ventilation observations	X	X	X	X	X	X	X					
Static respiratory compliance		X		X								
Combined open lung procedure		X*	X*	X*	X*	X*						

* Only for patients randomised to PHARLAP treatment group (combined open lung procedure)

Assessments/ Procedures	Pre Randomisation/ Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6 till liberation of mechanical ventilation	ICU discharge	Hospital discharge	Follow-up 28 days	Follow-up 90 days	Follow-up 6 months
Sputum sample (BAL)		X		X								
Blood sample		X		X								
Adverse events		X	X	X	X	X	X	X				
Serious adverse events		X	X	X	X	X	X	X	X			
Survival status								X	X	X	X	
$SF36V_2$												X
EQ5D												X

APPENDIX 4: APACHE II SEVERITY OF DISEASE CLASSIFICATION

APACHE II CALCULATION WORKSHEET

The APACHE II score is derived from 3 scoring systems: **Part A** – Acute Physiology Score, **Part B** – Age Points, **Part C** – Chronic Health Points

Part A - Acute Physiology Score

For each of the 12 physiological variables, select the value **closest in time**, but prior, to the patient meeting the final entry criteria for inclusion into the study (**T0** hours). Enter the value in the right hand column.

For exact non-integer data that is not found in any of the given ranges, round the figure up or down to the nearest whole number. Eg, 44 years and 3 months is rounded down to ≤ 44 years and assigned 0 points; a calculated MAP of 129.7 is rounded up to 130 and assigned 3 points. For integers of xx**.**5 always round upwards. This is an arbitrary decision but must be followed for every patient to ensure consistency.

1. **Temperature** – this should be a core temperature measurement (rectal, tympanic, oesophageal or via PAC). Where this is not possible, add 0.5^0C to the oral or axillary temperature
2. If mean arterial pressure (**MAP**) is not calculated by monitoring equipment, use the manual sphygmomanometer recording of systolic (SBP) and diastolic blood pressure (DBP) to obtain MAP using this equation MAP = (DBP x 2) + SBP ÷ 3.
3. If the patient has an atrial arrhythmia, measure the ventricular response rate (R waves) only to record the heart rate.
4. *A – aD*O_2 is the difference between the calculated alveolar oxygen tension and the arterial oxygen tension. The alveolar oxygen tension is calculated by this equation: *A*O_2 = 713 x *Fi*O_2 – $PaCO_2$ x 1.25. The *Fi*O_2 here is expressed as a proportion of a unit. e.g. 100% *Fi*O_2 = 1 and 60% equals 0.6. If the *Fi*O_2 (inhaled oxygen concentration) is greater than 50%, record the most deranged value for the *A – aD*O_2. If the *Fi*O_2 is less than 50% record only the *Pa*O2 (arterial oxygen pressure). All measurements are in mmHg.
5. If ABGs have not been performed, choose the most deranged value for the serum venous bicarbonate (HCO_3) in place of the **arterial pH**
6. To obtain a score for the Glasgow Coma Scale (**GCS**) use the GCS worksheet provided and subtract the GCS score from 15 to arrive at a score on the APACHE worksheet.

Whenever possible, make an attempt to obtain a score for each physiological variable. If one of the 12 variables is not available, assign 0 points and make a note of this absence on the APACHE II worksheet. The assumption being made is that a test or measurement was not ordered because the status of the patient did not warrant investigation, rather than the data was missing.

To complete **Part B** – assign points to the age range that the patient fits in to. eg, a 48 year old patient would be assigned 2 points.

To complete **Part C** – first decide if the patient meets any of the criteria provided on the worksheet for a history of severe organ insufficiency or immunocompromised. If there is no history, assign 0 points. If there is a history, assign points depending on whether the patient is an non-operative emergency admission or an emergency post-operative admission

Finally, add the points recorded for each of the 3 parts and enter this total score at question 1.7 The minimum score is 0 and the maximum score is 71. Keep the completed APACHE II worksheet in the documentation folder for this patient. It may be used for quality assurance measures. You will therefore need to print your hospital ID, Patient Initials and Patient Study Number on the APACHE worksheet

BASELINE DATA	APACHE II Severity Of Disease Classification	Patient Study Number
		|__|__|__|__|__|__|

	PHYSIOLOGIC VARIABLE	High Abnormal Range					Low Abnormal Range				APS Scores
		+4	+3	+2	+1	0	+1	+2	+3	+4	
A. ACUTE PHYSIOLOGY SCORE (APS)	Temperature – rectal (° C)	≥ 41	39 – 40.9		38.5 – 38.9	36 – 38.4	34 - 35.9	32 – 33.9	30 – 31.9	≤ 29.9	
	Mean arterial pressure – mmHg	≥ 160	130 - 159	110 – 129		70 - 109		50 - 69		≤ 49	
	Heart rate (ventricular response)	≥ 180	140 – 179	110 – 139		70 - 109		55 - 69	40 - 54	≤ 39	
	Respiratory rate (non-ventilated or ventilated)	≥ 50	35 – 49		25 - 34	12 - 24	10 - 11	6 - 9		≤ 5	
	Oxygenation: A - aDO_2 or PaO_2(mmHg) a. if $FIO_2 \geq 0.5$ record A - aDO_2	> 500	350 – 499	200 – 349		< 200					
	b. if $FIO_2 < 0.5$ record only PaO_2					PO_2 -> 70	PO_2 61 - 71		PO_2 55- 60	PO_2 < 55	
	Arterial pH	≥ 7.7	7.6 – 7.69		7.5 – 7.59	7.33 – 7.49		7.25 – 7.32	7.15 – 7.24	< 7.15	
	Serum sodium (mMol/L)	≥ 180	160 – 179	155 – 159	150 - 154	130 - 149		120 - 129	111 - 119	≤ 110	
	Serum potassium (mMol/L)	≥ 7	6 – 6.9		5.5 – 5.9	3.5 – 5.4	3 – 3.4	2.5 – 2.9		≤ 2.5	
	Serum creatinine (mMol/L) (double point score for acute renal failure)	≥ 0.300	0.171-0.299	0.121-0.17		0.05-0.12		< 0.05			
	Haematocrit (%)	≥ 60		50 – 59.9	46 – 49.9	30 – 45.9		20 – 29.9		< 20	
	White blood count (total/mm^3) (in 1,000s)	≥ 40		20 – 39.9	15 – 19.9	3 – 14.9		1 – 2.9		< 1	
	Glasgow Coma Score (GCS) (Score = 15 minus actual GCS)										
	Serum HCO_3 (venous – mMol/L) **(Only use this if no ABGs available)**	≥52	41 – 51.9		32 – 40.9	22 – 31.9		18 – 21.9	15 – 17.9	<15	

B. AGE POINTS

Assign points to age as follows:

Age (yrs)	Points
☐ ≤ 44	0
☐ 45–54	2
☐ 55–64	3
☐ 65–74	5
☐ ≥ 75	6

C. CHRONIC HEALTH POINTS

If patient has history of severe organ system insufficiency or is immuno–compromised, assign points as follows:	Points
☐ **a.** for non-operative or emergency post-operative patients	5
☐ **b.** for elective post-operative patients	2

DEFINITIONS: Organ insufficiency or immuno-compromised state must have been evident **prior** to this hospital admission and conform to the following criteria:

LIVER	Biopsy proven cirrhosis & documented portal hypertension (PH); episodes of upper GI bleeding due to PH; or prior episodes of hepatic failure/encephalopathy/coma
RENAL	Receiving chronic dialysis
CARDIOVASCULAR	New York Heart Association Class IV
RESPIRATORY	Chronic restrictive, obstructive or vascular disease resulting in severe exercise restriction (i.e. unable to climb stairs, perform household duties); or documented chronic hypoxia hypercapnia, 2° polycythemia, severe pulmonary hypertension (>40mmHg) or respirator dependency
IMMUNOCOMPROMISED	Patient has received therapy that suppresses resistance to infection, eg. immuno-suppression, chemotherapy, radiotherapy, long term or recent high dose steroids, or has a disease sufficiently advanced to suppress resistance to infection (eg leukaemia, lymphoma, AIDS)

APACHE II SCORE - a sum of:	**A.** APS points =____	**B.** Age points =____	**C.** Chronic Health points = ____	**Sum of A + B + C = _____** (0 to 71)

*For **intubated** patients use verbal scoring column allocated*

Best Verbal Response		**"Verbal " Intubated**		**Best Motor Response**		**Best Eye Opening**	
5	Orientated	5	Orientated	6	Obeys	4	Spontaneous
4	Confused	3	In Between	5	Localises	3	To Command
3	Inappropriate	1	No Response	4	Flexion – Withd.	2	To Pain
2	Incomprehensible			3	Flexion – Decort.	1	No Response
1	No Response			2	Extension		
				1	No Response		

APPENDIX 5: SHORT FORM 36V2 AUSTRALIAN VERSION

INSTRUCTIONS:

Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by filling in the bubble that best represents your response.

Example:

This is for your review. Do not answer this question. The questionnaire begins with question 1 below.

For each question you will be asked to fill in a bubble in each line, like this:

How strongly do you agree or disagree with each of the following statements?

	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
a) I enjoy listening to music.	○	●	○	○	○
b) I enjoy reading magazines.	●	○	○	○	○

Please begin answering the questions now.

---

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
○	○	○	○	○

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
○	○	○	○	○

Please turn the page and continue.

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a)	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	○	○	○
b)	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○	○	○
c)	Lifting or carrying groceries	○	○	○
d)	Climbing several flights of stairs	○	○	○
e)	Climbing one flight of stairs	○	○	○
f)	Bending, kneeling, or stooping	○	○	○
g)	Walking more than a kilometre	○	○	○
h)	Walking several hundred metres	○	○	○
i)	Walking one hundred metres	○	○	○
j)	Bathing or dressing yourself	○	○	○

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a)	Cut down on the amount of time you spent on work or other activities	○	○	○	○	○
b)	Accomplished less than you would like	○	○	○	○	○
c)	Were limited in the kind of work or other activities	○	○	○	○	○
d)	Had difficulty performing the work or other activities (for example, it took extra effort)	○	○	○	○	○

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a)	Cut down on the amount of time you spent on work or other activities	○	○	○	○	○
b)	Accomplished less than you would like	○	○	○	○	○
c)	Did work or other activities less carefully than usual	○	○	○	○	○

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
○	○	○	○	○

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
○	○	○	○	○	○

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
○	○	○	○	○

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a)	did you feel full of life?	○	○	○	○	○
b)	have you been very nervous?	○	○	○	○	○
c)	have you felt so down in the dumps that nothing could cheer you up?	○	○	○	○	○
d)	have you felt calm and peaceful?	○	○	○	○	○
e)	did you have a lot of energy?	○	○	○	○	○
f)	have you felt downhearted and depressed?	○	○	○	○	○
g)	did you feel worn out?	○	○	○	○	○
h)	have you been happy?	○	○	○	○	○
i)	did you feel tired?	○	○	○	○	○

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
○	○	○	○	○

11. How TRUE or FALSE is each of the following statements for you?

		Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a)	I seem to get sick a little easier than other people	○	○	○	○	○
b)	I am as healthy as anybody I know	○	○	○	○	○
c)	I expect my health to get worse	○	○	○	○	○
d)	My health is excellent	○	○	○	○	○

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE!

OFFICE USE ONLY

Reason for questionnaire non-completion:

_____

APPENDIX 6: EQ5D (ENGLISH VERSION FOR AUSTRALIA)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking around	❑	PLEASE TICK
I have some problems in walking around	❑	ONE BOX
I am confined to bed	❑	

Personal Care

I have no problems with personal care	❑	PLEASE TICK
I have some problems washing or dressing myself	❑	ONE BOX
I am unable to wash or dress myself	❑	

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑	PLEASE TICK
I have some problems with performing my usual activities	❑	ONE BOX
I am unable to perform my usual activities	❑	

Pain/Discomfort

I have no pain or discomfort	❑	PLEASE TICK
I have moderate pain or discomfort	❑	ONE BOX
I have extreme pain or discomfort	❑	

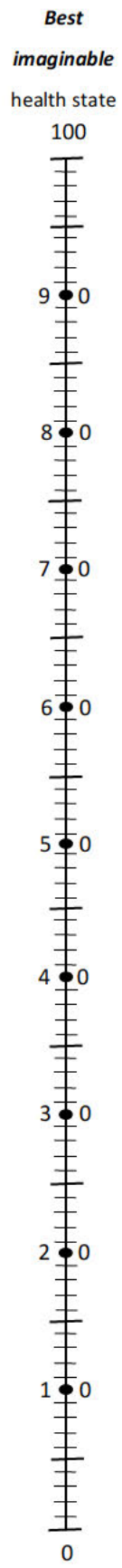
Anxiety/Depression

I am not anxious or depressed	❑	PLEASE TICK
I am moderately anxious or depressed	❑	ONE BOX
I am extremely anxious or depressed	❑	

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



APPENDIX 7: DIFFUSE VERSUS FOCAL ARDS SUBSTUDY

This is a study to determine if acute respiratory distress patients with different subtypes behave differently.

Background & rationale

Patients with different subtypes of ARDS (focal, diffuse and patchy (on Chest X Ray)) may behave differently with application of high vs low PEEP depending on the percent of recruitable lung and the amount of stress and strain during PEEP titration/ recruitment.

Patients with diffuse ARDS appear to have more recruitable lungs (1), have a higher inflection point and require higher PEEP levels for adequate recruitment without causing over-distension whereas patients with focal ARDS develop over-distension with higher levels of PEEP and have less recruitable lungs (2,3). Accordingly, in patients with a focal distribution of loss of aeration (i.e., with atelectatic dependent lobes coexisting with aerated nondependent lobes), the use of high PEEP levels (15–20 cm H2O) results in minimal alveolar recruitment in the dependent lobes but significant hyperinflation in the nondependent lung lobes. Patients with patchy ARDS lie in between the two above mentioned subgroups (Table 1).

	Incidence (n=71)	**Mortality rate**	**Primary ARDS**	**Compliance (ml cm H_2O^{-1})**	**Lower Inflection Point (cm H_2O)**
Diffuse	23% (16)	75%	82%	19±9	8.4±2
Focal	36% (26)	42%	50%	41± 21	4.6±2
Patchy	41% (29)	41%	79%	30±15	6.3±2.7

Table 1. Differences between the 3 subgroups of patients with ARDS (Puybasset etal) (2,4,5)

Patients can be identified *a priori* as either having focal, patchy or diffuse disease based on their chest radiograph at the time of ARDS diagnosis/ study inclusion. The PHARLAP study provides an excellent opportunity to prospectively examine the effect of PEEP and recruitment on lung injury in the different subgroups as there will measurement of blood and bronchoalveolar lavage cytokines levels as a part of the study.

Objectives

Aim

To investigate the effect of recruitment and high (PHARLAP) v low (conventional) PEEP levels on inflammatory markers in different subtypes of ARDS (based on CXR).

Hypothesis

Patients with diffuse ARDS, when randomized to the recruitment and high PEEP arm, will have lower inflammatory markers when compared to patients ventilated with conventional ARDSnet protocol (6) as used in the LOVS study (7).

Study outcome measures

Analyse the inflammatory outcomes based on the radiological type of ARDS.
Inflammatory markers will be measured by

- Baseline to day 3 change in IL-8 and IL-6 concentrations in non-bronchoscopic broncho-alveolar lavage
- Baseline to day 3 change in IL-8 and IL-6 concentrations in plasma

In addition we will also study the ARDS subgroups (based on CXR) on basis of response to recruitment (in the PHARLAP study group): i.e. recruitment manoeuvre responders - defined as patients who improve static lung compliance with recruitment manoeuvre (i.e. > 0 ml/cmH_2O) from baseline to day 2 and non-responders (Patients who do not improve static lung compliance) as patients with diffuse ARDS can be hypothesised to have more response with recruitment.

Study design

This will be a sub-study of all patients who are enrolled into the PHARLAP study. Informed consent is obtained for all patients enrolled in the PHARLAP study, the participant information and consent form includes details of the diffuse versus focal substudy.

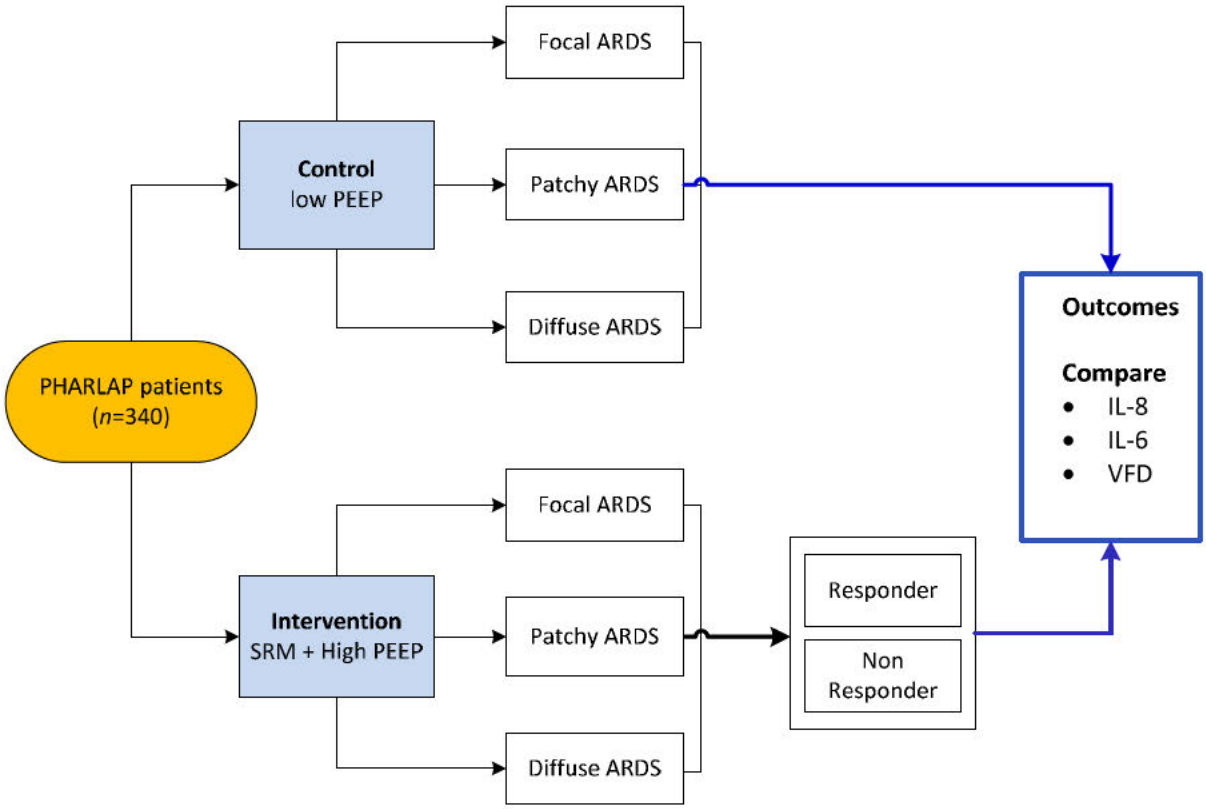
Methods

A chest radiograph at the time of ARDS onset (as determined by the study coordinator at the study site) will be de-identified, given a unique study number and saved to the PHARLAP database available for qualitative analysis post-hoc. Each patient will also have blood and BAL sample collected at baseline and day 3.

At the completion of the study the patients will be divided into predefined subgroups – focal, patchy and diffuse ARDS by independent radiologists. Additional data required for this sub study is the ventilator settings at the time of each CXR (PEEP, tidal volume, peak airway pressure and plateau pressure and respiratory rate) and blood gases.

Once patient's subgroups are identified (focal, patchy and diffuse) we will compare the subgroups of ARDS managed by intervention or control strategy with markers of lung injury (plasma and BAL IL8 and IL6 levels) and patient related outcomes such as ventilator free days and other clinical/patient centred efficacy outcomes (Primary and secondary outcomes of PHARLAP) (see study flow chart below).

Study Flow chart



Statistical considerations

As PHARLAP proposes to include 340 patients, based on previous studies (2,4,5,8) about one third of patients will fall into each group and this should still leave adequately sized groups of patients with focal, patchy and diffuse to study their influence on the PHARLAP primary outcome of number of ventilator free days at day 28 post randomisation, markers of inflammatory mediators, and several other secondary outcomes. With a total of 300 patients in the study based on data from Bersten et al (8) –personal communication we will likely get 80-100 patients per subtype, which would mean approximately 40 to 50 patient in each arm per subgroup. This should give us a reasonable sample size for each subgroup, and whilst mortality differences or VFDs may be unlikely, the potential for differences in other outcomes is reasonable, beside it will generate hypothesis for future studies.

We plan to analyse the outcomes of the study by utilising the general linear model with each outcome primary and secondary outcomes (PHARLAP - primary and secondary outcomes analysed separately as the dependent variable while ventilation strategy (PHARLAP / control), CXR coding (diffuse, focal, patchy) will be entered as independent factors. Interaction between ventilation strategy and the CXR coding will also be studied in the model. Post Hoc analysis will be done between the various CXR and ventilation subgroups (it will compare the outcomes of the CXR subgroups (diffuse, patchy and focal) within and among the PHARLAP and control group).

Funding

Diffuse versus focal substudy is supported by a $34 950 grant (ANZCA) for procurement of the Chest X rays, cost of independent radiological scoring, statistical advice and salary support for a research assistant based at the ANZIC-RC.

Publications

A separate publication following the main publication will be completed in the name of the PHARLAP investigators led by Shailesh Bihari and the PHARLAP writing committee.

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