# Optimising Positive End Expiratory Pressure in mechanical Ventilation using Pulmonary Elastance:

# A Randomised Controlled Trial



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**Pulmonary Model-based Decision Support to Optimise ARDS/ ALI Care**

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# Clinical Utilisation of Respiratory Elastance: the CURE Study – Optimisng PEEP in People on mechanical ventilation

**1.0 Study Administration**

**1.1 The Steering Committee**

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**Roles and Responsibilities**

* Management of study resources and liaison with funding bodies
* Project management
* Clinical protocol development
* Software development
* Protocol training
* Clinical trial monitoring
* Documentation
* Data management
* Data analysis and publications
* Organisation of meetings

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**Roles and Responsibilities**

* Data analysis and publications
* Organisation of meeting
* Advice on data analysis and publications

**1.3 Independent Data Monitoring Committee (DMC)**

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**Roles and Responsibilities**

* Documentation
* Data safety monitoring
* Advice on clinical protocol development
* Clinical trial progress assessment
* Organisation of meeting

For more details, refer to DMC charter.

**1.4 Independent Advisory and Supporting Members (International)**

Dr Thomas Desaive1

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**Roles and Responsibilities**

* Advice on software development
* Advice on documentation
* Advice on data management

**1.5 Christchurch Hospital Intensive Care Unit**

Christchurch hospital intensive care unit clinicians, nurses and technicians

**Roles and Responsibilities**

* Clinical trial implementation
* Clinical trial progress assessment

**2.0 Abbreviations**

ARDS - Acute respiratory distress syndrome

AE - Adverse events

ALI - Acute lung injury

ANZCTR - Australian New Zealand clinical trial registry

APACHE III - Acute physiology and chronic health evaluation III

AUC - Area under the curve

CO2 - Carbon dioxide

CURE - Clinical utilisation of respiratory elastance

DMC - Data monitoring committee

FiO2 - Fraction of inspired oxygenation

HDEC - Health and disability ethics committee

HRC - Health research council

ICU - Intensive care unit

LoMV - Length of mechanical ventilation

MAP - Mean arterial pressure

MaxRM - Maximum recruitment manoeuvre

MBV - Model-based mechanical ventilation

MV - Mechanical ventilation

NZ - New Zealand

P/F - Partial pressure of arterial oxygen / Fraction of Inspired Oxygenation

PaO2 - Partial pressure of arterial oxygen

PEEP - Positive end expiratory pressure

PulMoDS - Pulmonary model-based decision support to optimise ARDS/ ALI care

PUMP - Pressure adjustment and monitoring procedure

RCT - Randomised controlled trial

RM - Recruitment manoeuvre

SAE - Serious adverse events

SIMV - Synchronous intermittent mandatory ventilation

SpO2 - Oxygen Saturation

SPV - Standard practice ventilation

VILI - Ventilator induced lung injury

*Vt* - Tidal volume

**3.0 Introduction**

**3.1 Background**

Mechanical ventilation (MV) is a core and costly intensive care unit (ICU) therapy affecting up to 50% of ICU patients (~800 patients per year in Christchurch and 8000 per year in New Zealand (NZ)) ([ANZICS, 2010](#_ENREF_1), [Esteban et al., 2000](#_ENREF_12), [Dasta et al., 2005](#_ENREF_10)). Its primary goal is to support breathing of patient with respiratory failure, such as acute lung injury (ALI)/ acute respiratory distress syndrome (ARDS), maximising recruitment of lung units using added pressure to enable recovery, without damaging healthy lung units ([Mertens et al., 2009](#_ENREF_20)). However, while there is agreement that lower tidal volumes are preferred ([The Acute Respiratory Distress Syndrome Network, 2000](#_ENREF_28), [Girard and Bernard, 2007](#_ENREF_14)), there are no guidelines (and many conflicting trial results ([de Matos et al., 2012](#_ENREF_11), [Borges et al., 2006](#_ENREF_2))) for optimising the level of positive end expiratory pressure (PEEP) or added pressure. Typically, lower PEEP is considered better ([Hickling et al., 1990](#_ENREF_16), [Gattinoni et al., 2010](#_ENREF_13)), but can lead to increased cases of oxygen desaturation and hypoxemia (MV failure) ([Brower et al., 2004](#_ENREF_4), [Guerin, 2011](#_ENREF_15)). The result is a difficult problem of balancing added pressure and risk, as current tools and methods cannot provide insight into patient-specific response to PEEP ([Sundaresan and Chase, 2011](#_ENREF_24)).

As a result, patient care can be variable and costly ([Dasta et al., 2005](#_ENREF_10)), affecting patient-centred quality of care and clinical outcomes ([Chase et al., 2011](#_ENREF_6)). In particular, ventilated patients stay 70% longer in ICU and cost 140% more ([Dasta et al., 2005](#_ENREF_10)) than non-MV patients, indicating the potential for improving care. The main problem is the ALI/ARDS lung is very heterogeneous with significant inter- and intra- patient variability. Thus, what works for one patient may lead to ventilator induced lung injury (VILI) in another. The current standard of care is to perform an invasive recruitment manoeuvre to determine how best to titrate care ([Malbouisson et al., 2001](#_ENREF_19)). Thus, optimising MV management requires a means of assessing patient-specific lung condition and patient-specific response to MV therapy using a model-based approach, to account for these variabilities and optimise treatment without excessive clinical effort or recruitment manoeuvres.

Currently, several new model-based metrics for assessing patient-specific lung elastance ([Chiew et al., 2012](#_ENREF_9), [Chiew et al., 2011](#_ENREF_8), [Chiew et al., 2015](#_ENREF_7)), recruitment ([Sundaresan et al., 2009](#_ENREF_26), [Sundaresan et al., 2011a](#_ENREF_23)), and recruitment and lung volume response to MV ([Sundaresan et al., 2011b](#_ENREF_25)) have been developed. Importantly, they all offer insight into patient-specific condition that is not available via typical static surrogate estimates ([Lucangelo et al., 2007](#_ENREF_18), [Brochard et al., 2012](#_ENREF_3)), and, equally, they can be estimated breath-to-breath, and monitored as a surrogate of patient condition, as well as potentially being used to guide therapy ([Chiew et al., 2011](#_ENREF_8), [Sundaresan et al., 2011a](#_ENREF_23)). These models all offer the potential to guide MV therapy choices, have all been individually clinically validated, but have not yet been used to prospectively guide therapy directly ([Chiew et al., 2011](#_ENREF_8), [Sundaresan et al., 2011a](#_ENREF_23)). This clinical trial seeks to prove their potential in direct clinical use.

**3.2 Study Hypotheses**

The use of Model-based ventilation (MBV) can potentially improve patient quality of care and reduce length of mechanical ventilation (LoMV), and thus reduces mortality and cost in critically ill patients. Specifically, we hypothesise that MBV will reduce Length of MV (LoMV) and the number of desaturation events (MV therapy failure) compared to ‘standard’ practice ventilation (SPV) – improving quality of care and outcomes.

**3.3 Study Objective and Settings**

**3.3.1 Objective**

This study will be conducted in the Christchurch Hospital, Intensive care unit. The two-arm randomised controlled trial (RCT) will compare model-based ventilation (MBV) with standard practice ventilation (SPV) directly on matched cohorts of patients using recently implemented software technology ([Szlavecz et al., 2014](#_ENREF_27)). The goal is to assess the impact of model-based MV optimisation on clinical outcomes and patient-centred quality of care metrics. This two-arm RCT is named Clinical Utilisation of Respiratory Elastance: the CURE Study – Optimising Positive End Expiratory Pressure in mechanical Ventilation using Pulmonary Elastance: A Randomised Controlled Trial.

**3.3.2 Two-arm Randomised Controlled Trial**

For the duration of patients being supported with invasive mechanical ventilation, patients will be randomised to interventional treatment (Model-based ventilation, MBV) or control treatment (Standard practice ventilation, SPV).

* **SPV**: Control group: Receive current standard of care in the participating hospital, including tidal volumes of *Vt* ~ 6ml/ kg ([The Acute Respiratory Distress Syndrome Network, 2000](#_ENREF_28)), and the same measurements defined. PEEP and MV will thus be guided by clinicians per standard.
* **MBV**: Intervention group: MV guided by clinicians using computers and models to set PEEP and guide care. The models use real-time, readily available measurements of pressure and flow from the ventilator. MBV will use the model-based metrics (Minimal lung elastance during PEEP titration (Elung and Edrs model) ([Chiew et al., 2011](#_ENREF_8), [Chiew et al., 2012](#_ENREF_9))) to guide care.

The details of the clinical protocol for each group are described in Section 4.0.

**3.3.3 Trial Sample Size**

A power analysis was performed using retrospective data collected from the Intensive care unit Christchurch Hospital. Based on the analysis, CURE RCT is designed as Two-arm randomised control trial with 320 patients (160 patients per arm in 3 years).

The analysis was performed using patients’ data from year 2011 to 2014 who were admitted to the ICU needing mechanical ventilation support. It was found that approximately more than 900 patients were eligible for the study of 4 year period. A minimum effective sample size of 160 per arm is required to identify a 25% reduction in median Length of Mechanical Ventilation (LoMV) with a power of 80% and one-sided significance level of 5%. Thus, a sample size of 160 patients in 3-year period in the Christchurch ICU, based on retrospective that likely meet inclusion criteria. See Appendix A shows for the sample size analysis.

**3.4 Study Outcomes**

The proposed research will, for the first time, clearly define model based ventilation for best possible outcome in critically ill patients. They directly address the HRC goals:

* By providing the knowledge and methods make care more patient-specific and timely to optimise treatment and **improve outcomes** for a large cohort critically ill patients
* By **improving understanding of the patho-physiological basis** **of critical illness** via what we will learn about the hourly and daily evolution of ARDS/ALI through this study.

**3.4.1 Outcomes Measurements:**

**Primary**

* Area under the curve (AUC) of the Partial pressure of arterial oxygen / Fraction of inspired oxygen ratio (PaO2/ FiO2) over the period of mechanical ventilation.
* Number of desaturation events measured as Peripheral capillary oxygen saturation less than 88% (SpO2 < 88%).
* Length of mechanical ventilation (LoMV).

**Secondary**

* Ventilator free days (VFD) (28 days).
* AUC of SpO2 / FiO2 over the period of mechanical ventilation.
* Chest X-ray Index scores over time.

A difference in primary outcomes will show the impact of MBV compared to SPV. No difference would show that enhanced, model-based metrics of patient-specific condition have no effect on patient-centered or clinical outcomes. *Either outcome will yield clinical guidance*. The analysis procedure for the outcome measures are detailed in Section 5.5.

**3.4.2 Interim Study and Stopping Rules**

Interim and stopping rules is set using ICU mortality as outcome (90 days). If the mortality rate of the intervention group is significantly different to the control group and the numbers of patients allow 80% power, the trial will be terminated. The difference the will need to be observed according to certain group sample sizes is shown in Figure (left) below.



**Figure: (Left)** Sample sizes per arm required to detect a difference in mortality rate between groups with 80% power. **(Right)** The corresponding false positive rate at each sample sizes.

In this study, the expected control group mortality is at 20%.

Example of how to use this graph is shown below.

**Example 1:**

At power of 80%, at the sample size per arm of 50. The absolute mortality difference found in the Figure (left) is approximately 27%. If mortality rate is 20% for Control group, the mortality rate for Intervention will be 47% to detect a difference with significance at p<0.05 and power 80%. Thus, at sample size 50 per arm, Control group will observed 10 deaths and Intervention group will observed 24 deaths. The corresponding false positive rate is less than 0.1%, indicating that there is less than 0.1% that we can detect a difference when there is no difference. If the mortality rate observed in intervention is equal or higher than this mortality rate during interim analysis. This finding will notified to the clinical investigators and data monitoring committee and suggest for early trial termination.

**Example 2:**

At power of 80%, at the sample size per arm of 100. The absolute mortality difference found in the Figure (left) is 19%. If mortality rate is 20% for Control group, the mortality rate for Intervention will be 39% to detect a difference with significance. Thus, at sample size 100 per arm, Control group will observed 20 deaths and Intervention group will observed 39 deaths. The corresponding false positive rate is less than 0.1%, indicating that there is less than 0.1% that we can detect a difference when there is no difference. If the mortality rate observed in intervention is equal or higher than this mortality rate during interim analysis. This finding will notified to the clinical investigators and data monitoring committee and suggest for early trial termination.

The sample size and stopping rule analysis are attached in Appendix A1.

The first interim will be carried out at sample sizes of 50 per arm. Subsequent interim study will be carried out when patient recruitment reach 75, 100 and 125 per arm.

**4.0 Clinical Protocol**

This trial compares 2 cohorts of invasive mechanically ventilated patients with Acute Respiratory Distress Syndrome (ARDS): **1) Standard Practice Ventilation (SPV) (Control Group)** and **2) Model-Based Ventilation (MBV) (Intervention Group)** in a two-arm randomised control trial.

1. Patients randomised for MBV will have mechanical ventilation (MV) PEEP selected at inflection lung elastance after performing a PEEP titration process. This optimal PEEP is selected by a computer. This PEEP level is designed to maximise lung recruitment and avoid minimise excess pressure or lung over distension ([Carvalho et al., 2007](#_ENREF_5), [Suarez-Sipmann et al., 2007](#_ENREF_22), [Lambermont et al., 2008](#_ENREF_17), [Chiew et al., 2011](#_ENREF_8), [Chiew et al., 2015](#_ENREF_7)).
2. To select the MBV optimal PEEP, patients on MBV will undergo maximum recruitment manoeuvre (RM) and PEEP Adjustment and Monitoring Procedure (PUMP).
3. Patients randomised for SPV will have mechanical ventilation PEEP selected based on the current existing standard of care as performed by the attending clinicians.

**4.1 Block Randomisation**

In this study, block randomisation will be used. The randomisation will be performed in blocks, where the block sizes are generated using a randomisation program written in JAVA. The program will randomly assign patients into either a control group or intervention group through a random block size (block size is either 4, 6, 8, 10 patients).

**4.2 Ethics and Dissemination**

Ethics approval has been filed with the Southern New Zealand Health and Disability Ethics Committee (HDEC). The CURE RCT trial clinical protocol and data usage has been granted (Reference number: 14STH132). The CURE pilot trial is also registered in the Australian New Zealand Clinical Trial Registry (ACTRN12614001069640).

**4.3 Informed and Delay Consent**

Standard ventilation practice includes manoeuvres to increase lung recruitment. However, these clinical practices are widely variable and ad-hoc. The recruitment techniques to improve oxygenation and mechanics of ventilation in this proposed study are within the scope of standard ICU clinical practice. The protocols used in this study will standardise these existing interventions to recruit lung volume and titrate PEEP.

Study participants will be unable to consent to participation in this study prior to enrolment as they will be sedated and mechanically ventilated. It is also equally important that patients be commenced in one or the other arm of the RCT at the beginning of MV to ensure a fair comparison and the integrity of the results. We propose to use a delayed consent process which will randomly assign patients to either the intervention or control groups. Retrospective opinions from family members as to whether they believe the patient would wish to participate in the study will be sought as soon as practicable after the start of mechanical ventilation. In our pilot study (Ethics reference: 13/STH/84) it has often not been possible to speak with family members within 48 hours of the start of mechanical ventilation. By this time, it may be too late to see any benefit in optimising lung mechanics over a patient’s stay. We believe the most critical time to maximise lung recruitment is in the first 3-6 hours of the mechanical ventilation, and equally, over the first 1-2 days of MV may also be critical.

This approach has been utilised in several previous, large (RCT) ICU studies such as the NICE study (AKY/04/09/237) the RENAL study (MEC05/10/131) and the CHEST study (MEC09/07/080). We discuss the study with family/whanau and provide them with an information sheet and opportunities to answer any questions about the study. An opinion from the family/whanau will be sought as to whether they believe their relative/friend/whanau would agree to participation. If the family/whanau agrees to their relative/friend/whanau participating in the study, they will be asked to sign a statement.

In cases where the family/whanau cannot attend the hospital to sign the statement, their opinion will be obtained by telephone in the first instance. Information about the study will either be made available by emailing them the information sheet and contacting them later by telephone, or the information sheet will be read to them over the telephone. The telephone conversation(s) and their opinions will be documented in the patient’s medical record. As soon as the family/whanau is able to attend the hospital, they will be asked to sign the statement. If the family are not able to sign a statement during the patient’s time in the ICU, we would give them the option of printing out the statement, signing it, and mailing/emailing/faxing it back to us.

If the family/whanau do not support for their relative/ friend’s continued participation, the relative/friend will cease participation in the study. However, researchers will seek agreement from family/whanau to use information related to mechanical ventilation collected up until that point. If the family/whanau does not agree to this request, all information obtained for the study will be destroyed.

The researchers will seek permission form patients who have recovered sufficiently to provide to (i) continue in the study, or (ii) use data already collected. Patients who do not provide permission will be withdrawn from the study and all data collected will be destroyed. The corresponding project notice, locality authorisation, Maori consultation and ethics approval letters are attached as Appendices.

Appendix B: Project notice

Appendix C: Ethics approval

Appendix D: Locality HDEC authorisation report

Appendix E: Maori Consultation

The patient, relative, friend, family/whanau information sheets and the corresponding consent forms are included in as Appendices.

Appendix F: Relative, friend, family/whanau information sheet

Appendix G: Patient information sheet

Appendix H: Relative and Patient consent form (Clinical trial and data usage)

Appendix I: Follow up letter for consent (In case of no consenting in the Hospital)

**4.4 Participation Criteria**

**4.4.1 Inclusion Criteria:**

1. Patients requiring invasive mechanical ventilation (MV) (Intubation or tracheotomy).
2. Patients with PF [oxygen partial pressure to fraction of inspired oxygen] ratio < 300 mmHg)
3. Arterial line in situ.

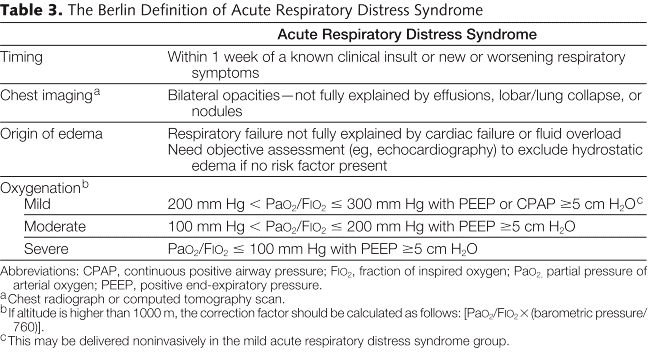
**4.4.2 Exclusion Criteria**

1. Patients who are likely to be discontinued from MV within 24 hours.
2. Patients with age < 16.
3. Any medical condition associated with a clinical suspicion of raised intracranial pressure and/or a measured intracranial pressure ≥ 20 cmH2O.
4. Patients who have a high spinal cord injury with loss of motor function and/ or have significant weakness from any neurological disease.
5. Patients who have a barotrauma (pneumothorax, pneumomediastinum, subcutaneous emphysema or any intercostal catheter for the treatment of air leak).
6. Patients who have asthma as the primary presenting condition or a history of significant chronic obstructive pulmonary disease.
7. Patients who are moribund and/or not expected to survive for > 72 hours.
8. Patients who have already received MV for > 48 hours (including time spent ventilated in a referring unit).
9. Lack of clinical equipoise by intensive care unit (ICU) medical staff managing the patient.

\* Patients who are readmitted to the ICU and requiring invasive MV, within 28 days from the first day entering to the trial, will be allocated to the same trial arm. If the readmission day is after 28 days, the patient will be excluded from the trial.

\* Patients diagnosed with all acute respiratory distress syndrome (ARDS) severity as per the Berlin Definition ([The ARDS Definition Task Force, 2012](#_ENREF_29)) will also be analysed in a subgroup analysis as ARDS is likely to be a secondary diagnostic. Based on retrospective data of 4 years, there are only less than 20 patients were coded with APACHE III diagnostic code which is far too little.

A screening form as shown in Appendix J will be completed prior to trial commencement.



**4.4.3 Termination Criteria**

During a recruitment manoeuvre (RM), there are known impacts on the cardiovascular system and respiratory system. Specifically, there is a fall in cardiac output, or blood pressure, or desaturation due to increases of pulmonary shunt. These changes will be anticipated and, inotropes, fluid loading and oxygen therapies maybe initiated to these changes in advance of the RM.

1. Recruitment manoeuvre will not be initiated if the patient care may be compromised from increased sedation and/or use of muscle relaxants.
2. At any time during a recruitment manoeuvre, the RM is terminated if any of the changes below persist for more than 3 minutes:
   1. Desaturation with SpO2 less than 88%.
   2. New bradycardia (reduction heart rate by 20% and < 60 beats per minute) or,
   3. New tachycardia (increase of heart rate by 20% and > 140 beats per minute) or,
   4. New arrhythmia leading to (2) or (3) above or,
   5. New hypotension (reduction in MAP by 30% or MAP < 60 mmHg).
3. Lack of clinical equipoise by the clinician; e.g. when a patient has a low blood pressure and is thought to be intolerant of PEEP changes.

MBV will be stopped and will revert to current standard of care when there is lack of clinical equipoise by the clinician. The clinical reason will be recorded.

**4.5 Patient Preparation for CURE RCT:**

1. For the length of mechanical ventilation, patients will be randomised to SPV (Control) or MBV (Intervention) using a block randomisation software (4, 6, 8 or 10 patients per block).
2. All patients enrolled are to be ventilated using Puritan Bennett PB840 ventilator (Covidien, Boulder, CO, USA) using synchronized intermittent mandatory ventilation (SIMV) with volume control ventilation.
3. Patients who are already ventilated using Dräger V500 ventilator (Drägerwerk AG & Co. Lübeck, Germany) will have their ventilator changed to Puritan Bennett 840 for the trial.

**4.5.1 Procedures for Control group, SPV**

1. For patients randomised for SPV (control), they will receive current standard of care, which limits plateau pressure less than or equal to 30 cmH2O while maximising tidal volume, *Vt* = 6~8 ml/kg based on predicted body weight using arm demispan. The arm demispan is measured from sternal notch to base of 4th finger and use the look-up table at the bedside to calculate this range.
2. Ventilation rate should be adjusted between 12 and 20 breaths per minute. Maintain the plateau-PEEP pressure to ≤ 30 cmH2O. If necessary, the tidal volume may be reduced as low as 4 ml/kg and the respiratory rate increased up to 30 breaths per minute. Do not attempt to normalise CO2 by exceeding these guidelines.
3. Positive end expiratory pressure (PEEP) and MV will be selected by clinicians as per standard practice.
4. All mechanically ventilated patients enrolled in the trial should have their fraction of inspired oxygen (FiO2) titrated to achieve the following pulse oximetry saturations.
   1. Aim for a saturation of 88-95%. For higher FiO2 use target lower end of the aim.

For example: if FiO2 of 0.6 target saturation 88-90%.

1. The FiO2 should only be increased (above 0.21) if these targets are not met. Use 5% increments starting with a FiO2 = 0.25. To avoid toggling between two FiO2 levels, please allow about 10-15 minutes before changing the FiO2. There will be natural variation in SpO2 levels. Choose the best FiO22 to keep the saturation 88-95**% of the time** within the above targets.
2. It is very important to standardise oxygen titration to pulse oximetry recordings to ensure robustness of outcomes. Upper and lower SpO2 alarm limits will be set to ensure these guidelines are follower. There is no upper SpO2 limit if the FiO2 is <30%.
3. All participants should be managed with usual nursing cares. In particular, in the participants are paralysed or receiving high levels of support from the ventilator, they should be rolled from supine to left-side down to right-side down etc. because this procedure significant changes in recruitment/ de-recruitment and possibly contributed to ventilator induced lung injury.

***Note:***

De-recruitment leading to transient hypoxaemia is common in ventilated patient. Frequently this occurs just after a patient has been turned. The right lung is 10% larger than the left and each lung is variably affected by the inflammatory process. This unknown variability combined with inadequate PEEP may cause significant changes in recruitment on turning leading to desaturation. Thus, it is important to avoid large changes in posture if possible.

Please carefully titrate inspired oxygen to changes in saturation. The only way we can readily detect changes in V/Q mismatch at the bedside is to see how much oxygen is required to maintain a consistent saturation, so small changes in titrated oxygen will correspond to changes in recruitment. Thus, an increase of 0.1 or 10% may indicate inadequate PEEP or deteriorating lung function (or both). The easiest way to sort this out is to re-recruit the lungs.

**4.5.2 Procedures for Intervention group, MBV**

1. For patients included for MBV (intervention), the PEEP and MV will be guided by clinicians using bedside computers while maintaining tidal volume and FiO2 similar to the procedure in Control group, SPV.
2. Patients in MBV will initially undergo a maximum recruitment manoeuvre (MaxRM), and subsequently with PEEP adjUsted Monitoring Procedure (PUMP).
   1. Before the RM, patients must be sedated and paralyzed with muscle relaxants to prevent spontaneous breathing efforts.
   2. The first RM when the patient is included in the study is a Maximum Recruitment Manoeuvre (MaxRM). This is done at the beginning of the trial by clinicians and only repeated if clinically indicated. Other PEEP adjustments will be a modification of the MaxRM. The **P**EEP adj**U**stment and **M**onitoring **P**rocedure is referred to as a ‘PUMP’, where the change of PEEP is -2 cmH2O to +6 cmH2O of the current PEEP setting. The PUMP may be performed by either medical or nursing staff trained in the technique.
   3. PEEP adjustments in the study (PUMP) will stop
      1. Patient’s FiO2 ≤ 0.4 **and**
      2. The patient has fully transitioned to spontaneous breathing; using pressure support mode **and**
      3. Arterial blood oxygen, PaO2 ≥ 60 mmHg at FiO2 ≤ 0.4 for the last 24 hours. **or**
      4. After 10 days from study enrolment.
      5. At the discretion of the clinician, for example:
         1. New neurological condition.
         2. The patient is awake and breathing normally without evidence of respiratory distress, where sedation with (or without) paralysis is not considered to be in the best interest of the patient.
         3. If the FiO2 is increased to ≥0.45 or more during spontaneous breathing within 8 days of enrolment they will be sedated, re-paralysed and a maximum recruitment manoeuvre will be carried out. This will be followed by PEEP titrations as per protocol.
3. Data will be collected continuously until the patient is disconnected from the ventilator.

**4.6 How to conduct Recruitment Manoeuvres (MaxRM and PUMP)**

**4.6.1 Maximum Recruitment Manoeuvre (MaxRM)**

Patients randomised into MBV will immediately receive the following intervention involving:

1. Patient airway cuff pressure is increased to 50 cmH2O to prevent leaks during maximum recruitment manoeuvre (RM).
2. The peak airway pressure alarm on the ventilator is set to 55 cmH2O.
3. Prior to the MaxRM, a muscle relaxant with appropriate sedation (eg. fentanyl and/or propofol) are co-administered.
4. During the MaxRM, PEEP is initially increased in steps of 4 cmH2O above the baseline PEEP level (selected by clinicians) until Peak airway pressure reaches (PIP) ≥ 50 cmH2O.
5. Each PEEP is maintained for 10-15 breathing cycles for calculation of Elastance before a subsequent PEEP increase.
6. After reaching PIP of ≥ 50 cmH2O, PEEP is reduced by 4 cmH2O steps until initial PEEP setting.
7. Once PEEP has returned to the initial setting, a second RM is performed with PEEP increase steps of 4 cmH2O to the same PIP used in the first RM. PEEP is then decreased by steps of 2 cmH2O until the optimal PEEP level has been obtained. This PEEP will be recommended by bedside computer when the elastance decrement is ≤ 5% of the previous value (See diagram for example of PEEP selection).
8. **If the intensive care clinicians do not feel the recommended PEEP level is appropriate, they will have the discretion to select a PEEP of their choice**. **The clinician will be prompted to record the reasons they have not followed the recommendations**.
9. This process will be performed at the beginning of the trial, and only repeated at the clinician’s discretion, if there has been a possible loss of recruitment, e.g. following a disconnection form the ventilator.
10. At the end of the MaxRM, the cuff pressure is reduced back to ~30 cmH2O and the ventilator alarms is set to back to initial setting.

|  |  |
| --- | --- |
| **Example 1** | **Example 2** |
| Example2 | Example1 |
| **Recommend PEEP = 14 cmH2O** | **Recommend PEEP = 15 cmH2O** |

**4.6.2 PEEP Adjustment and Monitoring Procedure (PUMP)**

This procedure is performed when:

1. When the patient is turned to supine position\* or
2. Every subsequent 6 hours after the first RM, or
3. If the FiO2 is adjusted by ≥10% or more, or
4. Any time at the clinician’s discretion or,

Whichever of condition (1) – (4) occurs first triggers a PUMP procedure.

\*Usual clinical practice is to turn patients left side to supine to right side every three hours

The procedures for the above PEEP adjustment and monitoring manoeuvres (PUMPs) are as follows:

1. If there are spontaneous breathing efforts as indicated by high elastance variability. The clinicians should sedate or paralyse the patient to breathe with synchrony with the ventilator prior to any MaxRM or PUMP.
2. If the FiO2 has remained constant, decrease PEEP by 2 cmH2O and start the PUMP procedure. Increase PEEP in 2 steps of 4 cmH2O with 10-15 breathing cycles at each step before lowering in 4 cmH2O decrements to -2 cmH2O of baseline PEEP.
3. If the FiO2 is increased by ≥10% (**as per condition 3 above**), start the PUMP at the current PEEP and proceed as per step 2 finishing up on the original PEEP.
4. The Bedside computer will recommend the optimal PEEP ([Chiew et al., 2011](#_ENREF_8), [Chiew et al., 2012](#_ENREF_9), [Chiew et al., 2015](#_ENREF_7)) at the end of the second PUMP Recruitment Manoeuvre.
5. If the intensive care clinicians do not feel the recommended PEEP level is appropriate, they will have the discretion to select a PEEP of their choice. The clinician will be prompted to record the reasons they have not follower the recommendations.

**4.7 Cases of Ventilator Dyssynchrony**

Ventilator dyssynchrony occurs when a patient's spontaneous respiratory efforts are not synchronous with the ventilator. This commonly causes agitation and respiratory distress, which is often described as “fighting the ventilator”. Dyssynchrony should be considered in patients with increased respiratory efforts, unexplained agitation, tachycardia, or sweating. Ventilator wave forms can be used to identify dyssynchrony as shown in Figure 1 below.



**Pressure**

**Flow**

**Time**

**Negative deflection in circuit pressure**

**Breath stacking resulting from volume starvation**

Figure 1: Dyssynchrony in a volume-controlled mode produces negative deflections in the pressure time wave form.

Synchronised intermittent mandatory ventilation (SIMV), does not accommodate to changes in inspiratory demand. Patients frequently can “out-breathe” the ventilator, which may cause the circuit pressure to become very negative. Flow and volume starvation are the main reasons for dyssynchrony.

In pressure controlled modes, such as Bi-Level, dyssynchrony is seen as negative deflections (“M” waves) in the flow time waveform as shown in Figure 2. The airway pressure is controlled so will be minimally influenced by the patient.



**Pressure**

**Flow**

**Time**

**“M” wave in the flow time waveform**

Figure 2: An “M” wave is seen in the flow time waveform (flow starvation), which is followed by a spontaneous (pressure-supported) breath.

When dyssynchrony occurs in mechanically ventilated patients receiving a set respiratory rate this can be initially managed by increasing sedation. It may be necessary to use Bi-Level ventilation, which is better able to accommodate for variable and increased respiratory demands. However, in many cases it is preferable to use muscle relaxants intermittently to fully control their ventilation.

Only when the PEEP and the FiO2 are respectively less than (or equal to) 10 cmH2O and 0.4 should participants be trialled using assisted spontaneous breathing (ASB).

A note of caution: switching to spontaneous breathing too early, because of ventilator dyssynchrony, may paradoxically result in more agitation, as the patient becomes completely exhausted (see “Weaning Assessment”)

**4.8 Weaning assessment**

The weaning assessment should be triggered when a patient’s lungs and circulation are stable and recovering. The patient may be weaned to assisted spontaneous breathing (ASB) using pressure support or proportional assist ventilation (PAV) if ≥ **3 of the following are present**:

***Respiratory:***

* Respiratory rate (RR) (total) ≤ 25/ min
* Minute ventilation VE ≤ 150 ml/ kg/ min

***Cardiovascular:***

* Vasoactive infusion ≤ 10 mcg/ min
* Heart rate (HR) ≤ 130/ min

1. If the patient is comfortable and tolerating ASB, the PEEP and pressure support may be reduced after 12 hours; thereafter, they may proceed towards separation from mechanical ventilation (extubation, or CPAP via a tracheostomy).
2. During weaning on ASB, it is important to check that patients are not tiring and their gas exchange has not deteriorate. This check is required at least every two hours or sooner if there is reason to suspect failure to wean. If a patients fails the weaning assessment ***at any time*** they should be fully re-ventilated on SIMV using the last settings prior to weaning.
3. Patients should be mechanically ventilated for at least 12 hours before any new weaning assessment is made. This assessment will be carried out between 0800 hours to 1500 hours.
4. If the FiO2 ≥ 0.45, regardless whether patients still meet the criteria for weaning, they should be re-ventilated on the original protocol they were randomised to: either MBV or SPV. Patients will remain on their protocol until 10 days has elapsed since randomisation.
5. If the patient is in SPV group, select a clinically a clinically appropriate PEEP. Either SIMV (Volume controlled ventilation) or Bi-Level Ventilation may be used.
6. If the patients requires a PEEP of ≥ 15 cmH2O, a FiO2 ≥ 0.6 and SpO2 ≤ 90%, they may be considered for a maximum recruitment manoeuvre (MaxRM).
7. A MaxRM may be carried out if this thought to be in the best interests of the patient. See the Section 4.6.1 for the procedure for MaxRM.
8. Base on the patient’s response to the MaxRM, select a new PEEP. If the patient is poorly responsive to the first MaxRM, it may be repeated. However, some patients will not be responsive to recruitment manoeuvres; it is unhelpful to repeat these manoeuvres unless there is reason to suspect the lungs have become de-recruited, e.g. following a circuit disconnect and persistent de-saturation.
9. If the patient is still receiving mechanical ventilation after 10 days they will exit the protocols and managed according to standard unit care protocols.

**4.9 Simplified Guideline**

A summary of the full clinical protocol as detailed in section 4.0, CURE Study Guide, is attached at the end of the document as Appendix K. The overall protocol is simplified and this document is written in a form of a study guide for the purposed of clinicians and nursing training and immediate reference.

**5.0 Data Collection**

The following data are collected from the patient recruited into the CURE RCT.

**5.1 Patient Demographic and History**

1. Patient gender, height, weight and ethnicity.
2. Patient APACHE III diagnostic code.
3. Primary patient diagnosis contributing to ARDS or impaired lung function.
4. Secondary patient diagnosis contributing to ARDS or impaired lung function.
5. Relevant past medical history e.g. smoking, medication, cardiovascular disease.
6. Chest X-ray score: Murray Index ([Murray et al., 1988](#_ENREF_21)).

**5.2 CURE Software and Computer platform**

Data on patient airway pressure and flow generated from the mechanical ventilator will be recorded using the CURE Software (CURE Soft) provided for the RCT. The mechanical ventilator Puritan Bennett 840 (PB840) is connected to a computer platform where CURE Soft is installed. The computer platform used in this study is a GeChic On-Lap 1520I touch screen monitor connected to Intel NUC515RYH 5th Gen i5 NUC assembled with 8GB DDR3L and 256GB SATA SSD.

CURE Soft will collect the airway pressure and flow data from the commencement of the trial until patient is weaned from the mechanical ventilation or redrawn from the RCT and if the patient/family or whanau would not wish for any more data to be collected.

The following will be recorded directly from the ventilator using a data acquisition system for the duration of the trial:

1. Airway pressure - For estimating respiratory mechanics (elastance and resistance)
2. Air flow - For estimating respiratory mechanics (elastance and resistance)
3. FiO2 - For determining oxygen dose (or exposure) and calculation of PF ratios.

CURE Soft version 1.0.11 is available in open access journal BioMedical Engineering OnLine (<http://www.biomedical-engineering-online.com/content/13/1/140>). The current software version used in this trial is 1.0.23.

**5.3 BedMaster**

BedMaster (Excel Medical Electronics, Jupiter FL, USA) is a 3rd party software installed in the Christchurch Hospital ICU to provide electronic data extraction and storage from networked General Electric (GE) monitor. The following but not limited to the data listed below will be recorded from the ‘Bedmaster’ server for the duration of the trial:

1. SpO­2 - For recording desaturation events.
2. Blood pressure.
3. Heart rate.
4. End tidal CO2 (CO2 as routinely measured on the patient’s breath at the bedside).

**5.4 Patient Data Sheet and Arterial Blood Gases Information**

Patient data sheet are constantly updated as standard procedure in the ICU. The following but not limited to the data listed below will be recorded for the duration of the trial:

1. PCO2
2. PaO2 - For determining oxygen dose (or exposure) and calculation of PF ratios (2X daily)
3. Patient position - to account for data variation that results from patient position varying
4. Length of mechanical ventilation (LoMV) - As an indicator of long term condition of the patient
5. Amount of sedation - to account for possible data variation resulting from different sedatives
6. Length of ICU stay
7. All causes of ICU mortality (days till death up to 90 days)

**5.5 Confidentiality**

All patient data collected is de-identified using a patient numbering system. This system will be a simple incrementing scheme:

Patient randomised into intervention arm as: MBV-001, MBV-002, etc…

Patient randomised into control arm as: SPV-001, SPV-002, etc…

All data will be encrypted with VeraCript and stored in hard drive and backup in the cloud network service, DropBox, CURE RCT.

All steering committee members and designated researcher will have access and password to the encrypted data. \_\_\_\_ Dropbox ahchiew@hotmail.com this is cure trial \_\_\_\_

**5.6 Data Analysis**

**5.6.1 Primary and Secondary Outcome Data Analysis**

The primary outcome of the research is to assess the impact of Model-based ventilation (MBV) vs Standard Practice Ventilation (SPV). To do this we measure:

* **Clinical Outcomes** - measured by Length of MV (LoMV). LoMV is defined as the duration (in number of days) from the day when the patient is first included for the trial (MBV or SPV) to the day when the patient is discontinued from mechanical ventilation.
* **Patient-Centered Quality of Care** - measured by number of de-saturation events (NoD). NoD is defined as number of de-saturation events (NoD), where oxygen saturation (SpO2) is less than 90%, measured throughout the course of receiving SV o MBV.
* **Adequacy of Gas Exchange** - measured as area under the curve of PF ratio (AUC\_PF). PF ratio is defined as ratio of partial pressure of oxygen in the arterial blood (PaO2) divided by fraction of inspired oxygen (FiO2). AUC\_PF is the area under the curve of PF ratio measured throughout the course of receiving SPV o MBV.

As for secondary outcomes, we will assess the outcome quality of care using the following data:

* **Ventilation Free Days (VFD) -** measured by 28 days - Length of MV (LoMV). VFD includes the information of patients mortality and thus, changes the distribution of LoMV. This change is performed by modifying all LoMV > 28 to 28 days and any deceased patients’ LoMV to 28 days. Table below shows example of conversion:

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Status** | **LoMV (days)** | **VFD (days)** |
| **Patient A** | Alive | 16 | 28 - 16 = 12 |
| **Patient B** | Alive | 31 | 28 - 31 = -3 🡪 0 |
| **Patient C** | Alive | 1 | 28 – 1 = 27 |
| **Patient D** | Decease | 16 | 28 - 16 = 12 🡪 0 |
| **Patient E** | Decease | 35 | 28 - 35 = -7 🡪 0 |

* **Oxygen Saturation Assessment** - measured as area under the curve of SF ratio (AUC\_SF). SF ratio is defined as pulse oximeter oxygen saturation (SpO2) divided by fraction of inspired oxygen **(**FiO2). AUC\_SF is the area under the curve of SF ratio measured throughout the course of receiving SV o MBV.
* **Level of Recruitment -** measured as Chest X-ray Index (Subject to availability)
* The lung area is divided into 4 quadrants: 1) Left upper quadrant (LUQ), 2) Left lower quadrant (LLQ), 3) Right upper quadrant (RUQ) and 4) Right lower quadrant (RLQ). The Chest X-ray Index ranges from 0 to 4, where the number indicates the total number of consolidated alveolar quadrants.

**5.6.2 Specific Analysis**

The following shows the specific analysis that will be carried out in each collected data. In particular, the Lilliefors test will be used to assess normality of raw or log-transformed data. Assuming an approximately normal distribution, 2-sample t-tests (t-test) will be used to compare the distributions from the control and intervention groups. If the data appears to be from non-parametric distributions, the Mann-Whitney U (MW) and 2-sample Kolmogorov-Smirnov tests (KS-test) will be used to assess differences in location and shape, respectively of the distributions. P-values less than 0.05 will be considered to indicate statistically significant (differences in) results.

**A. Length of Mechanical Ventilation (LoMV):**

* Lilliefors test: Assess the distribution of LoMV for the control and intervention group.
* One tailed/ two tailed t-test/ log t-test or MW and KS test.

**B. Patient-Centered Quality of** **Care:**

* Total NoD is normalised by dividing the total of NoD for all days that the patient was on MV, by the total number of days on MV (|NoD|).
* Lilliefors test: Assess the distribution of NoD for the control and intervention group.
* 2-tailed t-test or MW and KS test depending on outcome of Lilliefors test.

**C. Area under curve of PaO2/FiO2 ratio** **over time (AUC\_PF):**

* Total AUC\_PF is normalised by the total number of hours on MV (|AUC\_PF|).
* Lilliefors test: Assess the distribution of AUC\_PF for the control and intervention group.
* 2-tailed t-test or MW and KS test depending on outcome of Lilliefors test.

**D. Ventilation Free Days (VFD):**

* Lilliefors test: Assess the distribution of VFD for the control and intervention group.
* One tailed/ two tailed t-test/ log t-test or MW and KS test.

**E. Area under curve of SpO2/FiO2 ratio over time (AUC\_SpO2):**

* Total AUC\_SpO2 is normalised by the total number of hours on MV (|AUC\_SPO2|).
* Lilliefors test: Assess the distribution of AUC\_SpO2 for the control and intervention group.
* 2-tailed t-test or MW and KS test depending on outcome of Lilliefors test.

**F. Chest X-ray Index:** Scores over time to assess level of recruitment (Subject to availability)

* Lilliefors test: Assess the distribution of Chest X-ray Index for the control and intervention group.
* 2-tailed t-test or MW compares the mean values of Chest X-ray Index for both groups.

Analysis performed on the data collected from CURE RCT is not limited to only the listed. Further analysis will be carried out as deemed necessary by the investigators. All analyses and data presentations will be carried out using MATLAB (The Mathworks, Natick, Massachusetts, USA), Microsoft Office tools and/ or other software deemed necessary by the investigators.

**5.6.3 Other**

Other data recorded in the trials will have their data analysed similar to and/ or other methods than the proposed methods noted in Section 5.6.2.

**6.0 Safety and Trial Monitoring**

**6.1 Data Monitoring Committee (DMC)**

An independent local Data Monitoring Committee (DMC) comprising experts in the clinical trials, biostatistics and intensive care medicine is established before patient enrolment to review all trial protocols, and oversee/advise this trial.

The DMC members are:

1. Associated Professor Katrina Sharples (Chair and Primary Reviewer)
2. Dr Mark Jeffrey
3. Professor Ngaire Kerse
4. Professor Thomas Lumley
5. Professor John McCall
6. Dr Colin McArthur
7. Dr Mark Webster
8. Ms Lana Lon (DMC Secretary)

The DMC will be forwarded a copy of all serious adverse events (SAE) reports as soon as they become available to the trial investigators. The DMC will review all SAE reports that they receive and report back to investigators if any further action is required.

**6.2 Adverse Events (AE)**

Adverse events (AEs) are defined as any untoward medical occurrence in a patient of investigation subject administered an investigational intervention and which does not necessarily have to have a causal relationship with this treatment.

It is recognised that the intensive care patient population will experience a number of common aberrations in laboratory values, signs and symptoms due to the severity of the underlying disease and the impact of standard therapies. These will not necessarily constitute an adverse event unless they required significant interventions or are considered to be of concern in the investigator’s clinical judgement.

**6.3 Serious Adverse Events (SAE)**

SAEs 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 untoward medical occurrence that:

* Results in death
* Life-threatening
* Prolongation of hospitalisation
* Results in disability and incapability

The baseline mortality of intensive care patients enrolled in the trials will be high due to the critical illness that has necessitated their ICU admission. They will frequently develop life-threatening organ failure(s) unrelated to study interventions and despite optimal management. Events that are a part of the natural history of the primary disease process or expected complications of critical illness will not be reported as serious adverse events in this trial.

Additionally, events already defined and reported as study outcomes e.g. mortality, re-admission to ICU, will not be labelled and reported separately as adverse events or SAEs unless they are considered to be causally related to the study intervention or are otherwise of concern in the investigator’s judgement.

**6.4 SAE Reporting**

Serious adverse events (SAE) which occur from the time of commencement of study will be reported to the principal investigator within 24 hours when the investigators becoming aware of the event. Minimum information to report will include:

* Nature of the event
* Commencement and cessation of the event
* An investigator’s opinion of the relationship between study involvement and the event (not related, unlikely, possibly, probably or definitely related).
* Whether treatment was required for the event and what treatment was administered.

All suspected unexpected serious adverse reactions (SUSARS) are to be reported to the DMC (via Secretary to the DMCC) no later than 5 working days after the event.

The SAE form as shown in **Appendix L** will be completed. The following are possible SAE diagnosis that may occur during the trial:

**Direct Consequence (known causes):**

* Air leak/pneumothorax
* Hypotension transient leading to cardiac arrest
* Desaturation transient leading to severe and prolonged

**Indirect Consequence (known causes):**

**Reaction to Muscle Relaxant or Increased Sedation**

* Hypotension or hypertension/ tachycardia (patient awake of increased CO2 due to under ventilation)
* Bradycardia
* Arrhythmia
* Anaphylaxis (allergic reaction)

**Operator Errors**

* Relates to operator error e.g. cuff over inflation (failure to deflate)
* Unintended protocol deviations (e.g. accidental increase in peak airway pressure during RM)

All adverse events are coded according to Common Terminology Criteria for Adverse Events (CTCAE) as per website:

<http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf>

**7.0 Patient Enrolment and Data Management**

The following shows the simplified flow chart of the patient enrolment into CURE RCT and data management chronological order. A detailed flow chart is attached in **Appendix M.**

**Patient admitted to ICU requiring invasive MV**

**Check eligibility**

**End**

**Block randomisation**

**Control (SPV)**

**Intervention (MBV)**

**Delayed consent**

**Trial Termination for any reason: Patient disconnect from MV due to recovery, Serious adverse events (SAE) etc.**

**Written informed consent signed by the family or participant for data usage**

**Data encrypted and stored**

**Patient consent, SAE reports, and other documentations stored in a repository**

**End**

**Written informed consent are obtained from the family/ relative/ Whanau after the initiation of the trial**

**If any SAE occurs, a SAE report is documented and reviewed by Data monitoring Committee**

**Not Eligible**

**Eligible**

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