**CURE Study Guide**

This trial compares 2 groups of invasive mechanically ventilated patients with Acute Respiratory Distress Syndrome (ARDS): **1)** Standard Practice Ventilation (SPV) (control) and **2)** Model-Based Ventilation (MBV) (intervention).

This study will assess the impact of a lung recruitment method, which uses lung stiffness (elastance) to estimate the best level of PEEP in patients with ARDS.

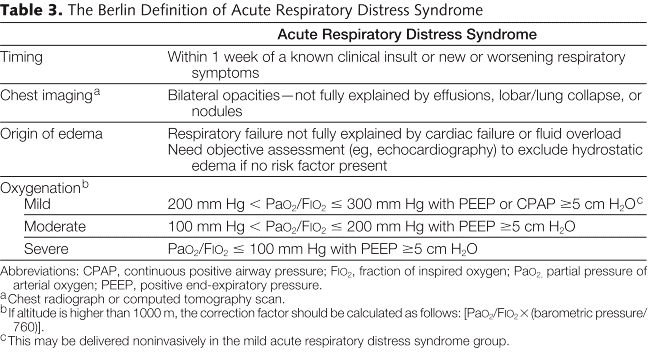
**Inclusion Criteria:**

**1**

All Patients with a **P/F ratio <300 mmHg** are eligible for enrolment

*Patients with a diagnosis of ARDS as defined by the Berlin definition will be separately analysed. The definitions are as follows:*

1. *Patients requiring invasive mechanical ventilation (MV) (Intubation or tracheotomy).*
2. *Patients diagnosed with all acute respiratory distress syndrome (ARDS) severity (PF [oxygen partial pressure to fraction of inspired oxygen] ratio <300 mmHg) as per the Berlin Definition (The ARDS Definition Task Force, A. 2012), by intensive care clinicians.*
3. *Arterial line in situ.*



*The ARDS Definition Task Force 2012*

**2**

**Exclusion criteria: (Not eligible for enrolment)**

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.

**Presumed Consent**

**3**

In an earlier pilot study in Christchurch Hospital ICU we found it could take up to 48 hours to gain agreement from families or whanau to allow patients to participate. Recruitment manoeuvres have also become standard practice in the management of some patients with ARDS. For these reasons the Southern Ethics Committee agreed “presumed consent” could be used to ensure that all patients could be enrolled within 4 hours of being mechanically ventilated. However, agreement from families or whanau should ideally be obtained within 48 hours. If the patient does not appear have any identifiable family or whanau and proxy consent is not be possible within the first few days, they should be withdrawn.

**SIMV or Bi-Level Ventilation and SpO2 Targets**

If patients require muscle relaxants to facilitate ventilation or they are moderately sedated and not making spontaneous breathing efforts they should be ventilated using **Bi-Level or SIMV-VC (volume controlled) ventilation**. However if spontaneous breathing efforts (e.g. triggering the ventilator) are present they should be ventilated on **Bi-Level Ventilation** (or assisted spontaneous breathing if they meet the weaning criteria)

Tidal volume should be set to 6-8 ml/ kg predicted body weight. Measure the patient’s demi span (sternal notch to base of 4th finger) and use the look-up table at the bedside to calculate this range.

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.

**SpO2 Targets**

All mechanically patients in both arms of the CURE study should have their inspired oxygen levels titrated to achieve the following pulse oximetry saturations.

**Aim for a saturation of 88-95%.**

**For higher FiO2 use target lower end of the aim.**

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 FiO2 to keep the saturation 88-95**% of the time** within the above targets.

**Randomisation**

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Please use a dedicated laptop within the ICU to randomise each patient. Follow the on-screen instructions.

All patients are randomised in blocks to ensure the enrolments in each arm of the study are very similar. Once the patient is randomised please start the protocol as soon as it is practicable. Ideally all eligible patients should be on protocol within 4 to 12 hours from the commencement of mechanical ventilation. Patients who have been ventilated more than 48 hours, including time spent in another hospital will be ineligible (see exclusions).

**6**

**Maximum Recruitment Manoeuvre (MaxRM)**

This is only to be carried out by senior medical staff (SMOs) or senior trainees who are familiar with this technique. Participants assigned to the CURE protocol will initially undergo a maximum recruitment manoeuvre. These will be carried out by SMOs or registrars/ MOs trained in the technique. The MaxRM is designed to safely increase the inspiratory pressure to a maximum airway pressure of greater than or equal to 50 cmH2O. The Max RM is run using the bedside computer, which is configured to receive data from the PB 840 ventilator. The CURE software currently only works with the Puritan Bennett 840 ventilator, but will be written for the Dräger ventilators shortly.

***Please refer to detailed instructions on how the MaxRM is performed in the appendix***

**Pre-recruitment checklist**

1. Reliable arterial line.
2. Haemodynamic stability (ensure the patient is optimally ‘filled’, i.e. there is adequate left ventricular preload).
3. Inflate ETT cuff to 50 cmH2O (Ensure the cuff is deflated to less than 30 cmH2O at the end of the procedure).
4. Sedation should be titrated up so the patient is not verbally responsive and has a loss of their eyelash reflex. Use both fentanyl increments and propofol to provide a ‘balanced’ deeper sedation level.
5. Give Rocuronium 0.6 – 1.0 mg / kg through a reliable iv; ensure the line is flushed afterwards.
6. Ensure there is ready access to atropine and adrenaline in the unlikely event of hypotension or anaphylaxis.

**7 4**

**Select new PEEP**

At the end of the MaxRM the clinician will be asked to set a new PEEP level, which is recommended by the CURE software. The clinician may either accept this computerised recommendation, or reject it (with a reason) if they feel the new PEEP level is inappropriate.

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**Ventilator dyssynchrony**

Ventilator dyssynchrony occurs when a patient's spontaneous respiratory efforts are not synchronised 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.

**Pressure**

**Flow**

**Time**

**Negative deflection in circuit pressure**

**Breath stacking resulting from volume starvation**

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

Synchronised intermittent mandatory ventilation (SIMV), does not accommodate the 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. The airway pressure is controlled so will be minimally influenced by the patient.

**Pressure**

**Flow**

**Time**

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

*Fig 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. If the patient is receiving SIMV-VCswitch to Bi-Level ventilation, which is better able to accommodate for variable and increased respiratory demands. However, in many cases it may be 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”).

**Usual care**

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**All** participants should be managed with usual nursing cares. In particular, if the participants are paralysed, or receiving high levels of support from the ventilator, they should be rolled from supine to left-side down, to supine to right-side down etc. It is very important participants are not rolled form left-side down to right-side down etc. because this produces significant changes in recruitment/de-recruitment and possibly contributes to ventilator induced lung injury.

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**Increasing oxygen requirements post recruitment**

De-recruitment leading to transient hypoxaemia is common in ventilated patients. 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 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.

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**P**EEP adj**U**stment and **M**onitoring **P**rocedure **(PUMP)**

This is only to be carried out by ICU medical or nursing staff who are familiar with this technique. This procedure is used to check the level of PEEP is appropriate to the patient’s (changing) condition. In particular, when the patient is turned there is often de-recruitment of the dependant lung if the level of PEEP is inadequate. Frequently nursing staff report patients de-saturate on turns or are worse on a particular side.

The PUMP is a mini-recruitment procedure designed to adjust the level PEEP up or down. It should be done every six hours or if there is any suggestion of de-recruitment (see ).

**10**

***Please refer to detailed instructions on how the PUMP is performed in the appendix.***

**Pre-PUMP checklist**

1. Reliable arterial line.
2. Haemodynamic stability (ensure the patient is optimally ‘filled’, i.e. there is adequate left ventricular preload).
3. Ensure the cuff is inflated to 30 cmH2O
4. Sedation should be titrated up so the patient is not verbally responsive and has a loss of their eyelash reflex. Use both fentanyl increments and propofol to provide a ‘balanced’ deeper sedation level.
5. If the patient is making spontaneous breathing efforts give Rocuronium 0.6-1.0 mg / kg through a reliable i.v.; ensure the line is flushed afterwards. This manoeuvre maybe carried out on a non-paralysed patient providing they are not making respiratory efforts. Note: Pancuronium may be substituted 4-8mg where appropriate. For example, in a patient who has got severe ARDS will likely to require muscle relaxants to facilitate MV for more than 24 hours.
6. Ensure there is ready access to atropine and adrenaline in the unlikely event of hypotension or anaphylaxis.

This decision box asks whether the current FiO2 is the lowest for the past six hours, of if there has been an improvement following a recent PUMP. In either case continue with PUMPs until the FiO2 is ≤ 0.4 ***and*** the PEEP ≤ 10 cmH2O. At this point a weaning assessment will be performed (see ).

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If there has been a deterioration in oxygenation as evidenced by an increase in FiO2 and /or failure to respond to a PUMP, another maximum recruitment manoeuvre (MaxRM) is required (see ).

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If the patient requires a FiO2 ≤ 0.4, PEEP ≤10 cmH2O they may be weaned (see weaning protocol).

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:

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***Respiratory:***

1. Respiratory Rate (RR) (total) ≤ 25 /min.
2. Minute ventilation VE ≤ 150 ml /kg /min.

***Cardiovascular:***

1. Vasoactive infusions ≤ 10 mcg /min.
2. Heart rate (HR) ≤ 130 /min.

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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).

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During weaning on ASB, it is important to check that patients are not tiring and their gas exchange has not deteriorated. This check is required at least every two hours or sooner if there is reason to suspect failure to wean. If a patient fails the weaning assessment ***at any time*** they should be fully re-ventilated on Bi-Level using the last settings prior to weaning.

**17**

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 and 1500 hours each day.

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:

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***CURE*** or ***Standard Practice***. Patients will remain on either protocol until 10 days has elapsed since randomisation.

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If the patient is randomised to standard practice ventilation (SPV), select a clinically appropriate PEEP. If patients require muscle relaxants to facilitate ventilation or they are moderately sedated and not making spontaneous breathing efforts they should be ventilated using **Bi-Level or SIMV-VC**. However, if spontaneous breathing efforts (e.g. triggering the ventilator) are present they should be ventilated on **Bi-Level Ventilation** (or assisted spontaneous breathing if they meet the weaning criteria)

Tidal volume should be set to 6-8 ml/ kg predicted body weight. Measure the patient’s demi span (sternal notch to base of 4th finger) and use the look-up table at the bedside to calculate this range.

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.

If the patient requires a PEEP of ≥ 15 cmH2O, a FiO2 ≥ O.6 and the SpO2 is ≤ 90% they may be considered for a maximum recruitment manoeuvre (MaxRM).

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A Max RM may be carried out if this is thought to be in the best interests of the patient.

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A non-protocolised MaxRM may be carried out by an SMO, MO or registrar familiar with the procedure.

***Please refer to detailed guidelines on performing a non-protocolised MaxRM. in the appendix***

**Pre-recruitment checklist**

1. Reliable arterial line.
2. Haemodynamic stability (ensure the patient is optimally ‘filled’, i.e. there is adequate left ventricular preload).
3. Inflate ETT cuff to 50cmH2O (Ensure the cuff is deflated to less than 30 cmH2O at the end of the procedure).
4. Sedation should be titrated up so the patient is not verbally responsive and has a loss of their eyelash reflex. Use both fentanyl increments and propofol to provide a ‘balanced’ deeper sedation level.
5. Give Rocuronium 0.6-1.0 mg / kg through a reliable i.v.; ensure the line is flushed afterwards.
6. Ensure there is ready access to atropine and adrenaline in the unlikely event of hypotension or anaphylaxis.

**24 3**

Based on the patient’s response to the MaxRM, select a new PEEP. (refer to detailed guidelines on performing a non-protocolised MaxRM. in the appendix) If the patient is poorly responsive to the first MaxRM, it may be repeated. However, some patients will not be responsive to repeated recruitment manoeuvres. it is therefore unhelpful to repeat these manoeuvres unless there is a *new* reason to suspect the lungs have become de-recruited, e.g. following a circuit disconnect and persistent de-saturation.

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If the patient requires an FiO2 ≤ 0.4, PEEP ≤10 cmH2O they may be weaned (see weaning protocol).

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If the patient is still receiving mechanical ventilation 10 days following randomisation they will exit the formal recruitment protocols and will be managed according to standard unit care protocols.

**APPENDIX**

**Maximum recruitment manoeuvre (MaxRM) on the CURE protocol**

Ensure each step of the pre-recruitment checklist (above) is followed.

The MaxRM is carried out in the **SIMV-VC (decelerating ramp) mode.** The tidal volume should be set to 6-8 mls /kg. If the plateau pressure exceeds 30 cmH2O, reduce the tidal volume so this level is not exceeded.

Ensure the CURE soft program is running.

Adjust the FiO2 before you start so the SpO2 is ≥ 92%. *This will provide a ‘buffer’ in the event of a de-saturation occurring during the RM. This is a very common event due to V/Q mismatch; blood preferentially shunts through non-aerated regions of the lung. Resistance to blood flow in the aerated pulmonary capillaries increases with higher alveolar pressure and volume, which reduces regional flow and oxygen uptake.*

Click on the tab **“Start Maximum Recruitment”** and follow the steps of the CURE protocol. For this MaxRM, the PEEP will be increased incrementally in steps of 4 cmH2O until the peak airway pressure is ≥50 cmH2O. It is then reduced in 4 cmH2O decrements until the original PEEP is reached. Adjust the FiO2 to keep the SpO2 ≥ 88% during the RM. If the SpO2 ≤ 85% for more than 2 minutes, cease increasing PEEP and immediately start reducing the PEEP in 4 cm H2O decrements to the original level.

You will then be prompted to repeat the MaxRM again. The CURE soft program will recommend a new PEEP.

*The new PEEP level corresponds to a point on the decremental part of the elastance curve, which is 5% above the minimal elastance. This is where the rate of reduction in lung stiffness begins to decrease and newly recruited lung units are beginning to collapse*.

**Elastance**

**(L/cm H2O)**

**The shaded area is a function of the amount of recruitment**

**<5% Δ of the previous elastance value elastance**

**Minimal elastance**

**PEEP (cmH2O)**

**Initial PEEP**

**Optimal PEEP**

If the Max RM has to be interrupted before the peak airway pressure is ≥50 cmH2O, the CURE software may still be able to make a recommendation based on the elastance changes during the decremental PEEP phase of the MaxRM. There may still be significant recruitment. The Max RM may be repeated at a later time.

**Non-protocolised Maximum recruitment manoeuvre (MaxRM) on the SPV (standard practice ventilation) protocol**

Ensure each step of the pre-recruitment checklist (above) is followed.

The MaxRM is carried out in the **SIMV-VC (decelerating ramp) mode.** The tidal volume should be set to 6-8 mls /kg. If the plateau pressure exceeds 30 cmH2O, reduce the tidal volume so this level is not exceeded.

*This manoeuvre should only be carried out if it is considered to be in the best interests of the patient, e.g. a person with a viral pneumonitis and severe hypoxaemia where evidence from case series suggest higher levels of PEEP are required to recruit the lung.*

Ensure the CURE soft program is running in the background. *The programme will record the patient’s respiratory mechanics for comparisons with the intervention arm of the study. No other action is required.*

Increase the PEEP in 4 cm H2O step (holding the PEEP for minimum of 30 s at each increment), until the maximum airway pressure is ≥ 50 cm H2O. Decrease the PEEP in 4 cm H2O steps holding the PEEP for at least 60 s at each decrement until either there is a decrease in SpO2 from the maximum SpO2 (obtained at anytime during the recruitment manoeuvre) OR the PEEP is ≥ 4cm above the initial PEEP.

*Setting the PEEP 4 cm H2O above the initial PEEP will generally increase the PEEP to about 20 cm H2O. This corresponds to the protocolised PEEP setting (second protocol) for an FiO2 0.5 to 0.8 in the high PEEP arm of the ARDS Clinical Trials Network Study: “Higher versus Lower Positive End-Expiratory Pressures in Patients with the Acute Respiratory Distress Syndrome”, N Engl J Med 2004; 351:327-336*

If the SpO2 ≤ 88%, for more than 2 min cease increasing PEEP and return the PEEP to the original level.

**P**EEP adj**U**stment and **M**onitoring **P**rocedure **(PUMP)**

*This is only carried out in the intervention arm of this study. This procedure is designed to check the level of PEEP is appropriate to the patient’s (changing) condition.*

Ensure each step of the pre-recruitment checklist (above) is followed.

The PUMP is carried out in the either **SIMV-VC.** If the patient is on Bi-Level then switch to SIMV-VCwith a tidal volume similar to the Bi Level mode. (6-8 mls /kg). Observe for any respiratory efforts. If respiratory efforts are present, sedate as appropriate and paralyse with Rocuronium 0.6 -1.0 mg /kg.

Ensure the CURE soft program is running.

Adjust the FiO2 before you start so the SpO2 is ≥ 92%.

Before a PUMP is started **reduce** the PEEP by 2cm H2O. Click on the tab **“Start PUMP”** and follow the steps of the CURE protocol. For the PUMP, the PEEP will be increased in 2 steps of 4 cmH2O and then reduced to the starting PEEP. These steps are then repeated. Adjust the FiO2 to keep the SpO2 ≥ 88% during the RM. If the SpO2 ≤ 85% for more than 2 minutes, cease increasing PEEP and immediately reduce the PEEP to the original level.

If the PUMP has to be interrupted, the CURE software may still be able to make a recommendation based on the elastance changes during the decremental PEEP phase of the PUMP manoeuvre. A desaturation event does not preclude PUMP manoeuvre at a later time.