Invasive Mechanical Ventilation (IMV) Strategies Domain

Protocol Summary, for protocol v2.0 dated: 15Aug2024
https://practicalplatform.org/domains/imvs

Primary Objective	Identify the IMV strategy that most effectively improves patient outcomes among a range of strategies including conventional lung-protective ventilation for patients with acute hypoxemic respiratory failure.
Design	An interventional, open-label, multi-arm adaptive platform RCT. This domain is planned to run perpetually as interventions are added, continued, or discontinued. Patients will be randomized equally between all interventions available at any given site and in that state. All sites will randomize to the control arm and to at least one other arm.
Eligible Patient States	1. Intubated patients, not on ECLS, with low normalized respiratory elastance (<2.5 cm H_2O/(mL/kg predicted body weight)) 2. Intubated patients, not on ECLS, with high normalized respiratory system elastance (≥2.5 cm H_2O/(mL/kg predicted body weight)) 3. Patients on ECLS

Interventions	1. Driving Pressure-Limited Ventilation (DPL) *(Excludes patient state #3 – Patients on ECLS)* → **Undergoing phase III evaluation at all sites**
	• Tidal volume and positive end-expiratory pressure adjusted to maintain static airway driving pressure ≤15 cm H_2O (during passive ventilation) and dynamic transpulmonary driving pressure ≤23 cm H_2O (during assisted ventilation; estimated using expiratory hold - Pocc)
	• Plateau airway pressure ≤35 cm H_2O
	2. Lung/Diaphragm-Protective Ventilation and Sedation (LDPVS) → **Currently in pilot/feasibility phase at a small number of sites**
	• Ventilation and sedation adjusted to initiate spontaneous breathing as early as possible while maintaining;
	  • Dynamic transpulmonary driving pressure ≤23 cm H_2O (during assisted ventilation)
	  • Moderate respiratory effort (Pocc –5 to –20 cm H_2O) (during assisted ventilation)
	3. Careful Ventilation in Acute Respiratory Distress Syndrome - CAVIARDS (CAV) → Undergoing phase III evaluation at select sites
	• PEEP selection is based on the lung recruitability as measured by the recruitment-to-inflation ratio and on the presence of airway closure and airway opening pressure. Tidal volume is limited as per usual recommendations.
	• When patients are triggering the ventilator in pressure support mode the respiratory drive estimated by P0.1 is maintained within a normal range (1.0-3.9 cmH2O).
	4. Conventional Lung-Protective Ventilation (LPV) (control)→ **Current Phase III comparator**
	• Tidal volume target of 6 mL/kg predicted body weight
	• Plateau airway pressure ≤30 cm H_2O

	Sites participating in CAVIARDS will be limited to those that routinely use one of the PEEP-FiO2 tables (low or high) of the ARDS Network, and are also limited to those that would have an arterial line inserted as per standard of care for this patient population. To support protocol implementation, we have developed a clinical decision support tool, available at: https://practical-trial.shinyapps.io/practical_app/
Outcome	The phase III primary outcome is Ventilator-Free-Days to Day 28 – analyzed as an ordinal outcome and assigning a value of –1 to patients who die in hospital. CAV Intervention – effect of CAV on 60-day mortality in comparison to comparator group (primary analysis conducted in separate CAVIARDS RCT) LDPVS Intervention - (1) effect of LDPVS on the probability of achieving lung/diaphragm-protective targets in comparison to the comparator groups; (2) effect of LDPVS on daily diaphragm thickness in comparison to comparator groups
Duration	Patients will receive their randomized intervention until the earlier of extubation or day 28. Longer-term outcomes will be collected remotely through 6-months post-randomization.
Sample Size	Sample size is not fixed – the DPL vs LPV comparison in phase III will be evaluated using a Bayesian hierarchical statistical model and will enrol up to 2000 patients total per state.