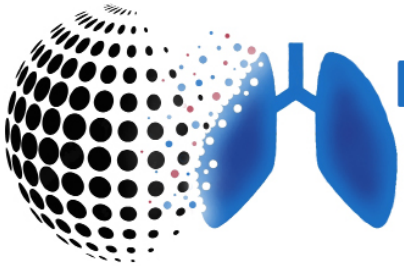

REMAP-CAP

Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

Domain-Specific Appendix:

Mechanical Ventilation

Acute Respiratory Failure Domain

REMAP-CAP: Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

Mechanical Ventilation Strategy Domain-Specific Appendix Version 1.0 dated 07 July 2020

Summary

In this domain of the REMAP-CAP trial, participants meeting the platform entry criteria who are intubated and are receiving invasive mechanical ventilation will be randomized to receive one of two mechanical ventilation strategies:

- Protocolized mechanical ventilation strategy
- Clinician-preferred mechanical ventilation strategy

At this participating site the following interventions have been selected within this domain:

☐ Protocolized mechanical ventilation strategy

☐ Clinician-preferred mechanical ventilation strategy

This DSA applies to the following states and/or stratum:

<table>
<tr><td>Stratum</td><td colspan="2">Pandemic infection suspected or proven (PISOP)</td><td>Pandemic infection neither suspected nor proven (PINSNP)</td></tr>
<tr><td>Core protocol documents</td><td colspan="2">REMAP-CAP Core Protocol + Pandemic Appendix, or REMAP-COVID Core Protocol</td><td>REMAP-CAP Core Protocol</td></tr>
<tr><td>Illness Severity State</td><td>Moderate State</td><td>Severe State</td><td>Severe State</td></tr>
<tr><td>Interventions available in this Domain + State</td><td>Domain not available</td><td>Protocolized IMV
Clinician preferred IMV</td><td>Protocolized IMV
Clinician preferred IMV</td></tr>
<tr><td>Interventions submitted for approval at this site</td><td>Domain not available</td><td>☐ Protocolized IMV
☐ Clinician preferred IMV</td><td>☐ Protocolized IMV
☐ Clinician preferred IMV</td></tr>
<tr><td rowspan="2">Interventions offered at this site in these locations</td><td>Ward</td><td>ICU</td><td>ICU</td><td>ICU</td></tr>
<tr><td>Domain not available</td><td>Domain not available</td><td>☐ Protocolized IMV
☐ Clinician preferred IMV</td><td>☐ Protocolized IMV
☐ Clinician preferred IMV</td></tr>
</table>

REMAP-CAP: Mechanical Ventilation Domain Strategy Summary	
Interventions	• Protocolized mechanical ventilation strategy • Clinician-preferred mechanical ventilation strategy
Unit-of-analysis, Strata, and States	This domain is analyzed in a ventilation statistical model which is separate to both the pandemic and the interpandemic statistical model. Within the ventilation statistical model there are two units-of-analysis corresponding to the Pandemic Infection Suspected or Proven (PISOP) stratum and the Pandemic Infection Neither Suspected nor Proven (PNSNP) stratum. An additional ordinal strata of PaO_2:FiO_2 ratio at time of randomization will be applied in analysis. Borrowing is permitted between states and stratum. Response adaptive randomization will not be applied during this preliminary phase.
Evaluable Treatment-by-Treatment Interactions	No interactions will be evaluated with any other domain.
Nesting	None
Timing of Reveal	Randomization with Immediate Reveal and Initiation
Inclusions	Inclusion criteria are those specified in the relevant core protocol documents. Domain-specific inclusion criteria are: • Receiving invasive mechanical ventilation • The most recent PaO_2:FiO_2 ratio obtained within the preceding 6 hours is less than 200 mmHg • Treating clinician expects the patient to still require invasive mechanical ventilation tomorrow • Treating clinician regards Protocolized Mechanical Ventilation Strategy or their preferred mode as (equally) appropriate for this patient.
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • More than 48 hours has elapsed since commencement of invasive mechanical ventilation. • The treating clinician believes that participation in this domain is not in the best interests of the patient.
Intervention-Specific Exclusions	Nil, not applicable.
Outcome Measures	Primary REMAP endpoint: refer to REMAP-CAP Core Protocol +/- PAtC and REMAP-COVID Core Protocol Secondary REMAP endpoints refer to REMAP-CAP Core Protocol +/- PAtC and REMAP-COVID Core Protocol. Secondary domain-specific endpoints (during hospitalization, censored 90 days from the date of enrollment): • Serious adverse events (SAE) as defined in core protocol documents • Administration of rescue therapies • Occurrence of barotrauma

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TABLE OF TABLES

1. ABBREVIATIONS

AC	Assist Control
APRV	Airway Pressure Release Ventilation
ARDS	Acute Respiratory Distress Syndrome
ARDSNet	Acute Respiratory Distress Syndrome Clinical Trial Network
ATS	American Thoracic Society
CAP	Community Acquired Pneumonia
COPD	Chronic Obstructive Pulmonary Disease
DSA	Domain-Specific Appendix
DSWG	Domain-Specific Working Group
DSMB	Data Safety and Monitoring Board
$ECCO_2R$	Extra-Corporeal Carbon Dioxide Removal
ECMO	Extra-Corporeal Membrane Oxygenation
ESICM	European Society of Intensive Care Medicine
EPVent2	Effect of titrating Positive end-expiratory pressure (PEEP) with an esophageal pressure-guided strategy vs. an empirical high PEEP-FiO2 strategy on death and days free from mechanical ventilation among patients with acute respiratory distress syndrome.
FiO2	Fraction of Inspired Oxygen
ICU	Intensive Care Unit
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
NMB	Neuromuscular Blockade
LUNG-SAFE	Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE
MODS	Multiple Organ Dysfunction Syndrome
PaO_2:FiO_2 Ratio	Ratio of Partial Pressure of Oxygen in Arterial Blood and Fraction of Inspired Oxygen Concentration
PBW	Predicted Body Weight
PEEP	Positive End-Expiratory Pressure
RAR	Response Adaptive Randomization
RCT	Randomized Controlled Trial
REMAP	Randomized, Embedded, Multifactorial Adaptive Platform trial

REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RSA	Region-Specific Appendix
SAE	Serious Adverse Event
SCCM	Society of Critical Care Medicine
SIMV	Synchronised Intermittent Mandatory Ventilation
Tv	Tidal Volume
VFD	Ventilator Free Days
VILI	Ventilator-Induced Lung Injury

2. PROTOCOL APPENDIX STRUCTURE

The structure of this protocol is different to that used for conventional trials because this trial is highly adaptive and the description of these adaptations is better understood and specified using a 'modular' protocol design. While, all adaptations are pre-specified, the structure of the protocol is designed to allow the trial to evolve over time, for example by the introduction of new domains or interventions or both (see glossary, Section 1.2 Core Protocol for definitions of these terms) and commencement of the trial in new geographical regions.

The protocol has multiple modules, in brief, comprising a Core Protocol (overview and design features of the study), a Statistical Analysis Appendix (details of the current statistical analysis plan and models) and Simulations Appendix (details of the current simulations of the REMAP), multiple Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain), and multiple Regions-Specific Appendices (RSA) (detailing regional management and governance).

The Core Protocol contains all information that is generic to the trial, irrespective of the regional location in which the trial is conducted and the domains or interventions that are being tested. The Core Protocol may be amended but it is anticipated that such amendments will be infrequent.

The Core Protocol does not contain information about the intervention(s), within each domain, because one of the trial adaptations is that domains and interventions will change over time. Information about interventions, within each domain, is covered in a DSA. These Appendices are anticipated to change over time, with removal and addition of options within an existing domain, at one level, and removal and addition of entire domains, at another level. Each modification to a DSA will be subject of a separate ethics application for approval.

The Core Protocol does not contain detailed information about the statistical analysis or simulations, because the analysis model will change overtime in accordance with the domain and intervention trial adaptations but this information is contained in the Statistical Analysis and Simulations Appendices. These Appendices are anticipated to change over time, as trial adaptations occur. Each modification will be subject to approval from the International Trial Steering Committee (ITSC) in conjunction with advice from the International Statistics Interest Group (ISIG) and the Data Safety and Monitoring Board (DSMB).

The Core Protocol also does not contain information that is specific to a particular region in which the trial is conducted, as the locations that participate in the trial are also anticipated to increase over time. Information that is specific to each region that conducts the trial is contained within a RSA. This

includes information related to local management, governance, and ethical and regulatory aspects. It is planned that, within each region, only that region's RSA, and any subsequent modifications, will be submitted for ethical review in that region.

The current version of the relevant Core Protocol (either REMAP-CAP Core Protocol +/- Pandemic Appendix or REMAP-COVID Core Protocol), DSAs, RSAs, and the Statistical Analysis Appendix is listed in the Protocol Summary and on the study website (www.remapcap.org).

3. MECHANICAL VENTILATION DOMAIN-SPECIFIC APPENDIX VERSION

The version of the Mechanical Ventilation Strategy Domain-Specific Appendix is in this document's header and on the cover page.

3.1. *Version history*

Version 1.0: Approved by the Mechanical Ventilation Domain-Specific Working Group (DSWG) on 7th July 2020

4. MECHANICAL VENTILATION DOMAIN-GOVERNANCE

4.1. *Domain members*

Chair:

Prof. Alistair Nichol

Members:

Prof. Derek Angus
Ms. Wilma van Bentum-Puijk
Dr. Lewis Campbell
Dr. Lennie Derde
Prof. Niall Ferguson
A/Prof. Timothy Girard
A/Prof. Ewan Goligher
Prof. Anthony Gordon
Mr. Cameron Green
Prof. Carol Hodgson

Prof. Peter Kruger

Prof. John Laffey

Dr. Edward Litton

Prof. John Marshall

Dr. Colin McArthur

Prof. Danny Mc Auley

Prof. Shay McGuiness

Prof. John Laffey

Dr. Neil Orford

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5. MECHANICAL VENTILATION DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

The Mechanical Ventilation Domain-Specific Working Group (DSWG) have read the appendix and authorize it as the official Mechanical Ventilation Domain-Specific Appendix for the study entitled REMAP-CAP. Signed on behalf of the committee,

Chair
Alistair Nichol

Date 07 July 2020

6. BACKGROUND AND RATIONALE

6.1. *Domain definition*

This is a domain within the REMAP-CAP platform to evaluate the effectiveness of alternative mechanical ventilation strategies in patients with severe Community-Acquired Pneumonia (CAP), including patients with suspected or proven COVID-19 infection, who are intubated and receiving mechanical ventilation.

This version of the ventilation DSA describes a preliminary phase of the domain. The duration of the preliminary phase is pre-specified. Information available during the preliminary phase will be used to design subsequent phases of the domain (which will be managed as a subsequent protocol amendment). This version of the ventilation DSA applies only to the preliminary phase but, so as to provide context, it does include identification of the goals, but not necessarily the methods that will be used, for subsequent phases.

6.2. *Introduction*

Severe CAP commonly results in respiratory failure, the need for intubation and the development of acute respiratory distress syndrome (ARDS) (Bellani et al., 2016). Pneumonia secondary to COVID-19 is associated with a high incidence of acute respiratory failure requiring intubation and mechanical ventilation (Richardson et al., 2020). Acute respiratory failure secondary to pneumonia manifests by impairment of transfer of oxygen from the atmosphere into the arterial blood of the patient or impairment of clearance of carbon dioxide from venous blood into the atmosphere or both (Bellani et al., 2016). In some patients the application of exogenous oxygen therapy is sufficient to maintain physiological homeostasis. However, in patients in whom the severity of respiratory failure is a threat to life, typical management is to institute invasive mechanical ventilation. This involves partial or complete substitution of the patient's own efforts to move gas in and out of the lungs by the application of invasive mechanical ventilation delivered via an endotracheal tube that connects the patient's trachea with a mechanical ventilator. The morbidity and mortality of CAP and COVID-19 pneumonia patients who require mechanical ventilation is high (Richardson et al., 2020, Bhatraju et al., 2020).

The interventions specified in this domain relate to the settings that are chosen by the treating clinician on the ventilator. It is universally accepted that the institution of invasive mechanical ventilation in a patient who would otherwise die from respiratory failure or ventilatory arrest is life-saving. However, there is little empiric evidence available to guide clinicians as to the optimal settings of the ventilator and whether the settings should be the same for all patients or differ for patients with definable characteristics. Furthermore, the lung physiology associated with pneumonia secondary to COVID-19 appears to have unique features and it is unclear if the optimal ventilatory strategy is different than for other forms of pneumonia.

We have outlined in detail the pathological changes in the lungs that occur secondary to CAP and the physiological components that are specified by the treating clinician when providing invasive mechanical ventilation (Appendix 1). Appendix 1, describes the significant heterogenicity in the severity and pattern of injury in CAP (irrespective of the causative organism) and that these patients are a high risk of VILI. In addition, we have summarized in detail the empiric evidence for the relationship between different options for invasive mechanical ventilation and patient outcomes. It is clear from Appendix 2, that there is significant heterogenicity in the severity and pattern of injury in severe CAP, including CAP caused by COVID-19, and that these patients are a high risk of ventilator-induced lung injury (VILI) and death. However, while many ventilation strategies currently exist, it is unlikely that one overarching strategy, will be appropriate for all mechanically ventilated patients with CAP. An immediate issue for the management of patients is that a great deal of the evidence derived from RCTs regarding mechanical ventilation in CAP, is derived solely from patients who progress to develop ARDS. Some, but not all patients in RCTs that enroll patients with ARDS have CAP and there is limited evidence from RCTs in patients with CAP who do not have ARDS. Current guidelines for CAP extrapolate from patients with ARDS to patients without ARDS. Guidelines for mechanical ventilation in patients with pneumonia secondary to COVID-19 have been released, but these are based solely on extrapolation from trials that enrolled patients with other causes of respiratory failure (Poston et al., 2020, Alhazzani et al., 2020a, Alhazzani et al., 2020b). There is also widespread non-adherence to current mechanical ventilation guidelines (Bellani et al., 2016). What is unclear is if this lack of adherence is due to a considered appraisal of the low level of evidence for many current recommendations, the patient severity illness or heterogenicity of disease.

6.3. *Current recommendations and variability among recommendations*

6.3.1. Current guideline recommendations for mechanical ventilation in patients with CAP

The American Thoracic Society (ATS), European Society of Intensive Care Medicine (ESICM), and Society of Critical Care Medicine (SCCM) have published consensus guidelines on mechanical ventilation in patients with ARDS that are directly relevant to those patients with CAP who have ARDS (Fan et al., 2017). The International Surviving Sepsis Campaign has also published consensus guidelines on mechanical ventilation in patients with sepsis (Rhodes et al., 2017), a proportion of whom will have CAP, including those who have developed ARDS. Both sets of guidelines make similar recommendations with regard to patients requiring mechanical ventilation.

The guidelines for ARDS (Fan et al., 2017) recommend patients receive mechanical ventilation with strategies that limit tidal volumes (4 to 8 ml/kg predicted body weight, PBW) and inspiratory pressures (plateau pressure below 30 cm H_2O). The initial tidal volume should be set at 6 ml/kg PBW and can be increased up to 8 ml/kg PBW if the patient is double triggering or if inspiratory pressure decreases below the set level of positive end-expiratory pressure (PEEP). This is a strong recommendation with there being moderate confidence in the quality of evidence (Fan et al., 2017). These guidelines identify substantial uncertainty regarding the question of how long this strategy should be used, before there is transition to spontaneous ventilation. It is noted that there may be benefit and harm from facilitating spontaneous ventilation as soon as possible, but that it is not always possible to achieve strict control of tidal volumes and inspiratory pressures in patients with ARDS while breathing spontaneously (Fan et al., 2017). There is evidence, derived from experimental animal studies, that abrogating early spontaneous ventilation may reduce ventilator-induced lung injury (Yoshida et al., 2012, Yoshida et al., 2013). The guidelines also note that there is need for randomized controlled trials (RCTs) to evaluate whether tidal volumes lower than 6 ml/kg PBW improve outcome. The guidelines also assess an observational study, derived from individual patient data from multiple RCTs, that reported that driving pressure (plateau pressure minus PEEP) was a better predictor of survival in patients with ARDS than either tidal volume or plateau pressure (Amato et al., 2015). However, as yet, there are not pilot RCTs that demonstrate feasibility of a strategy that targets driving pressure.

The Surviving Sepsis Campaign Guidelines (Rhodes et al., 2017) recommend a target tidal volume of 6 ml/kg PBW in patients with pneumonia who also have ARDS and regard this as a strong recommendation supported by high quality evidence. In patients without ARDS, low tidal volumes (4 to 6 ml/kg PBW) are also recommended for patients who do not have ARDS, although this is a weak recommendation supported only by low quality evidence (Rhodes et al., 2017). No recommendation

regarding duration of low tidal volume ventilation and transition to spontaneous ventilation is provided.

Both the ATS/ESICM/SCCM and Surviving Sepsis Campaign Guidelines recommend higher rather than lower PEEP in patients with ARDS with this recommendation rated as conditional supported by moderate evidence and weak supported by moderate quality evidence, respectively (Fan et al., 2017). This recommendation is based an individual patient meta-analysis of three RCTs that reported lower mortality (adjusted RR, 0.90; 95% CI, 0.81-1.00) (Briel et al., 2010). Higher and lower PEEP are not defined in either guideline, although the ATS/ESICM/SCCM guideline notes that operationalization of this recommendation is difficult because different methods were used to achieve higher PEEP in the pooled RCTs. The Surviving Sepsis Campaign Guidelines (Rhodes et al., 2017) provide three options for setting PEEP at a higher level comprising bedside measurement of compliance to obtain the best compliance or lowest driving pressure, to titrate PEEP upwards on a tidal volume of 6 ml/kg PBW until plateau pressure is 28 cmH_2O, or use of the PEEP:FiO2 table used in the RCTs of lower versus higher PEEP. The ATS/ESICM/SCCM Guidelines note that changes in PEEP will influence inspiratory plateau pressure but provides no advice about strategy when increases in PEEP result in an increase in plateau pressure to 30 cm H_2O or greater. Since the publication of these Guidelines the EPVent2 trial, which titrated PEEP according to transpulmonary pressure using a pressure monitor placed in the esophagus reported no improvement in outcome (Beitler et al., 2019). The Surviving Sepsis Campaign Guidelines do not provide a recommendation for patients with CAP who do not have ARDS regarding PEEP.

Both the ESICM and SCCM have produced guidelines to guide clinicians caring for critically ill patients with COVID-19 acute respiratory failure (Alhazzani et al., 2020a, Alhazzani et al., 2020b), but these are based on extrapolation from other forms of respiratory failure with only current evidence limited to case-series. Clinical trials to determine optimal ventilation strategy in patients with COVID-19 pneumonia have been initiated to try and address these clear evidence gaps (https://clinicaltrials.gov/ct2/show/NCT04306393).

6.3.2.Compliance with guidelines and heterogeneity of ventilatory practice

The above guidelines have been widely disseminated and many recommendations have become routine parts of clinical care globally (Levy et al., 2018). The adoption of many of the recommendations have become Key Performance Indicators and used as surrogates of quality in some healthcare intuitions. However, the heterogeneity of patients who require mechanical ventilation and the complex patient- ventilator interactions make the assessment of compliance with ventilation aspects of the guidelines problematic. While there is acknowledged uncertainty with regard to some

recommendations (i.e. Tv, plateau pressures and PEEP) in non-ARDs patients or those with mild ARDS, the guidelines are clearer on these recommendations for hypoxemic patients with moderate and severe ARDS. However, these recommendations, even for patients with moderate and severe ARDS, has not been translated into clinical practice. LUNGSAFE, was a large international observational study of mechanical ventilation practices in over 454 intensive care units (ICUs), included invasively mechanically ventilated patients with mild (n=722), moderate (n=1110) and severe (n=564) ARDS. The mean tidal volume was 7.76, 7.60 and 7.46 for mild, moderate and severe ARDS respectively. Many patients even with the most severe form of ARDS did not receive ventilation with tidal volume (Tv) < 6 ml /Kg / PBW. A significant number of patients had PEEP levels below the recommended high PEEP arm of ARDSnet, including patients with severe ARDS.

Furthermore, Esteban et al (Esteban et al., 2002, Esteban et al., 2013) conducted a number of observational studies in patients with ARDS receiving mechanical ventilation. While this data was a decade or more before the LUNGSAFE data, it again showed the use of higher than recommended Tv and lower than recommended PEEP. Furthermore, the compliance to trial ARDSnet protocols is poor also.

The reasons for non-adherence with guidelines have not been studied systematically. Our anecdotal understanding is that clinicians generally believe that outcomes for patients are better when the clinician can use modes of ventilation that do not set tidal volume or when the clinician can tailor the ventilator settings to the individual patient or both. It is also possible that the guidelines are not adhered to because the development of ARDS is not recognized or clinicians do not set plans to monitor and adjust tidal volume and PEEP. What is well established is that non-adherence to the guidelines is wide-spread.

6.3.3.Compliance with guidelines and outcome

Observational studies report better outcome with adherence to guidelines. In a cohort of 485 patients with hypoxemic respiratory failure secondary to ARDS, long-term mortality at 2-years was improved in patients compliant with lung protective ventilation during their ICU stay (Needham et al., 2012). However, observational studies may not be able to adjust for confounding, for example confounding caused by other aspects of treatment that may be better in units that can comply with guidelines. There are no RCTs that compare patients allocated to receive guideline recommended ventilation compared with a clinician-preferred ventilation strategy.

6.3.4. Within unit vs between unit variation

It is common practice in ICU trials in the critically ill to stratify randomization by site. This recognizes the many variations in clinical practice that occurs. While the bedside clinician on the day is the final arbiter of treatment of the patients, this approach recognizes that commonly such practices are more homogenous on a within unit level (within unit variation) than compared to the practice in another unit (between unit variation). This stratification approach hopes to balance out such differences as both groups of patients randomized in a trial would receive non-randomized aspects of care, on average, equally. In this study, we hope to use this within unit homogeneity towards their clinician - preferred method of mechanical ventilation (i.e. airway pressure release ventilation, APRV, titration of PEEP after lung recruitability assessment etc.) to group units with similar common preferred-mechanical ventilation practices. Furthermore, we will aim to determine *a priori* the ventilatory strategies that are common within an individual ICU.

6.4. *An analytic approach to determining optimal ventilation*

6.4.1. Scope of the problem

The empiric investigation of optimal ventilation is complicated by there being enormous variation in routine clinical practice. This variation occurs in relation to the ventilator setting, for which there are multiple axes with variation in each axis. A further four factors add to complexity. Firstly, there is heterogeneity of patient factors, which are potentially effect modifiers for ventilatory settings, including the possibility of divergent treatment effect (i.e. some settings are beneficial for some patients and harmful for other patients). Secondly, optimal ventilator settings may be dynamic, in that optimal settings vary at different times, in conjunction with evolution of underlying lung disease and other patient factors. Thirdly, some of the axes of ventilator settings may interact with each other. Fourth, the emergence of the novel COVID-19 acute respiratory failure may induce a nonclassical or heterogenous for of lung injury, which may respond differently to interventions that non-seasonal CAP.

Table 1 outlines some of the sources of variation in practice and potential patient factors that could modify treatment effect from different ventilator settings.

Table 1. Sources of variation in practice and potential patient factors that influence ventilator settings.

Ventilator Settings		
Ventilator Setting Characteristic	**Options and variable characteristic**	**Variable Characteristic**
Mandatory breaths-inspiratory Determinant	Pressure or Volume	Dichotomous and mutually exclusive

Mandatory breaths- How much inspiration set by volume	Set tidal volume	Continuous variable
Mandatory breaths- How much inspiration set by pressure	Set inspiratory pressure (above PEEP)	Continuous variable
How much PEEP	Set expiratory pressure	Continuous variable
Interplay between PEEP and inspiratory pressure	Delta P	Continuous variable
Spontaneous ventilation	Whether any spontaneous ventilation is permitted	Dichotomous and mutually exclusive
Mix of mandatory and spontaneous ventilation	Ratio of mandatory to spontaneous ventilation	Continuous variable
How much inspiratory support- spontaneous ventilation	Set inspiratory pressure (above PEEP)	Continuous variable
Target and achieved PaCO2	Determined by interplay between minute volume and lung pathology	Continuous variable
Airway pressure release ventilation	A mode, different to all other modes but with its own set of variable parameters	Dichotomous variable with all other types of ventilation and mutually exclusive
Sedation depth	Some ventilatory strategies only feasible in conjunction with deeper sedation	Ordinal scale, can vary substantially over time
Paralysis	Sometimes used as co-intervention. Some ventilatory strategies only feasible in conjunction with administration of paralysis	Dichotomous and mutually exclusive (but variable duration).
Patient Factors		
Name of patient characteristic	**Description of characteristic**	**Variable characteristics**
Nature of lung pathology	Nature of process affecting lungs including but not limited to fluid filling of alveoli, pus/inflammatory filling of alveoli, collapse of lung segments, interstitial fibrosis. Additional pathologies such as pulmonary embolism and airflow limitation.	Categories, non-mutually exclusive (i.e. patients can have more than one process)
Unilateral v bilateral disease	Whether pathological process is limited to one lung or present in both lungs	Dichotomous, mutually exclusive
ARDS v non-ARDS	Whether patient meets Berlin consensus criteria for ARDS. A subset of bilateral. Note: could compress this into a 3-category group of unilateral, bilateral non-ARDS, and ARDS (bilateral).	Dichotomous, mutually exclusive

P:F ratio	Ratio of partial pressure of oxygen in arterial blood to fractional inspired concentration of oxygen	Continuous variable
Lung compliance	Pressure:volume relationship. Some co-linearity between ARDS and non-ARDS.	Continuous variable
Other factors such as age, obesity, co-morbidity, frailty	Although not lung pathology factors these could modify treatment effect	
Pandemic COVID infection	COVID-19 infection or seasonal CAP	Dichotomous, mutually exclusive
Inflammatory phenotype	Hyper vs Hypo-inflammatory	Dichotomous, mutually exclusive

Ventilation also interacts with a range of additional therapeutic modalities, referred to as rescue therapies. These interventions which include ECMO, $ECCO_2R$, inhaled pulmonary vasodilators, and prone positioning are all capable of independently influencing outcome, may interact with ventilator strategies, and outcome may be influenced by both their use as well the timing of their initiation and the duration of their use.

As such, a consequence of the variation in ventilator settings (noting that some are continuous variables) combined with possibility of differential treatment effect depending on patient characteristics creates an overwhelming number of potentially testable variants of ventilatory strategy. Despite this capacity for variation, it is plausible that clinicians choose from particular combinations with greater frequency and in particular circumstances with regard to patient characteristics and timing. If so, this smaller number of patterns or strategies may create tractability of testable options.

Notwithstanding the potential variation, guidelines recommend a similar approach to ventilation, irrespective of the patient characteristics that might modify treatment effect. As such, a pragmatic first question to consider is whether there is a difference in outcome for following (or attempting to follow) the protocolized guideline-based strategy compared to allowing clinicians to choose the ventilator settings without, necessarily, following the guidelines. Supplementary questions include whether, when allocated to follow the guideline, adherence to the guideline can be achieved, when allowed to choose ventilator settings how frequently clinicians choose to adhere to the guideline, and to describe the distribution of thresholds of severity at which different clinicians are willing to randomize patients to the two interventions.

6.4.2. Protocolized guideline-recommended versus wild-type as first questions

It is proposed that the first question that will be assessed within this domain is to compare protocolized ventilation strategy, derived from the recommendations set by international guidelines, with the ventilatory strategy that the treating clinician would choose for the patient, including allowing the clinician to follow guidelines if that is their preference for patients, including patients with COVID-19. This allows the evaluation of several questions that are necessary for further adaptation of the domain. The first of these questions is a preliminary consideration of whether there is any difference in outcome between the two strategies. This is important because of widespread poor adherence to guideline-recommended strategy. Secondly, it allows assessment of adherence to guideline therapy in patients with severe CAP. We will aim to understand the barriers to adherence to various aspects of the guideline-based therapy. If adherence cannot be achieved consistently, and notwithstanding the recommendation of guidelines, an intervention that cannot be implemented after all reasonable barriers have be addressed may not be suitable for ongoing evaluation within the platform. Thirdly, by evaluation of the ventilatory strategies chosen by the clinician it establishes the frequency with which clinicians choose to follow the strategy recommended by guidelines and, when they choose not to follow guidelines, establishes the spectrum of 'wild-type' strategies that are in use. The latter information is useful for identifying strategies that are used commonly and might be capable of being defined as a deliverable intervention in subsequent phases of the ventilation domain. Fourth, randomization to these two options allows some assessment of the patient characteristics (i.e. the severity of illness threshold, as measured by a PaO_2/FiO_2, that each unit choses as the point of equipoise to randomize) that influence choice of ventilatory strategy and how these patient characteristics might act as effect modifiers for different treatment strategies.

Some possible outcomes from the preliminary phase include:

- A detailed description of current mechanical ventilation strategies used.
- Evaluation of separation in ventilatory parameters between protocolized and clinician-preferred strategies and identification of identifiably distinct patterns of ventilation within the clinician-preferred strategy.
- A preliminary evaluation of any difference in treatment effect between protocolized and clinician-preferred strategies
- A preliminary evaluation of any difference in treatment effect among identified strata
- If there is no separation between protocolized and clinician-preferred strategies, that protocolized should be the control group against which further specified variants are evaluated

- If clinician-preferred is superior to protocolized then further adaptation should involve testing identifiable variants with the spectrum of clinician-preferred options
- If there is separation between protocolized and clinician-preferred but there is not clear superiority of either strategy that it is reasonable to proceed with protocolized as a common control group and proceed with definable variants of clinical practice.
- If no difference (with limited statistical power after 400 patients) then further adaptation should proceed with protocolized as one intervention and one or more specified variants of clinician-preferred strategies as alternative interventions
- Evaluation of the distribution of threshold of severity at which randomization is acceptable to treating clinicians may be useful for adapting entry criteria or providing ordinal strata to which participating ICUs are willing to agree to ongoing randomization in patients

6.4.3. Isolation of testable strategies within heterogeneity of current practice

A critical component of the preliminary phase is the identification of definable ventilator strategies from within patients randomized to the clinician-preferred intervention. Several strategies may be considered. One approach is the use of qualitative methods to ask participating clinicians to describe their approach to ventilation for patients with different characteristics and the thresholds of physiological abnormality at which changes in strategy occur. Within some ICUs there is limited variation in strategy, i.e. there is a 'unit-level' approach to ventilation. Where an ICU believes that it follows a particular strategy this could be identified and described. Another approach would be to describe clinical thinking at the time ventilatory strategy is set and adjusted in patients who receive clinician-preferred ventilation. Lastly, data-driven approaches, such as machine learning, may be applied to the dataset of patients who receive clinician-preferred ventilation.

6.4.4. Analytic approaches to heterogeneity of current practice

The preliminary phase will enroll patients who meet the platform entry criteria of REMAP-CAP and are receiving invasive mechanical ventilation in an ICU. The study will collect information related to lung physiology, ventilation strategy and outcome.

Several different analytic approaches might be considered. Where possible, undertaking several multiple analytic approaches may be useful as consistency of results, across multiple analytic approaches, would increase confidence regarding the validity of conclusions. These possible approaches are outlined in each section. All approaches would be designed to demonstrate, if present, modification of treatment effect according to the presence of definable patient characteristics such

as presence of absence of ARDS, lung compliance, unilateral versus bilateral involvement, and P:F ratio.

6.4.4.1. Pre-specified unit-specific patterns of ventilatory strategy

Each participating ICU will be asked if they believe that there is a 'unit-level' approach to ventilatory strategy for patients that differs according to status with respect to the pandemic infection suspected or proven strata. This could include asking how the ICU believes it ventilates in a range of scenarios in patients:

- severe ARDS (i.e. bilateral infiltrates with poor lung compliance)
- less-severe ARDS (i.e. bilateral infiltrates with poor lung compliance and bilateral infiltrates without poor compliance)
- without ARDS (i.e. unilateral infiltrates but at range of different P:F ratios)

Where possible, strategies that are similar across multiple ICUs will be identified and be analyzed as a defined strategy. Where there is a belief that the ICU follows a particular strategy, participating ICUs, nested within a country, will be evaluated within a Bayesian Hierarchical Model as an explanatory variable. This includes permitting one or more participating ICUs to adopt their choice of a specific protocol for ventilation in patients with suspected or proven pandemic infection which will be identified as a defined strategy within the overall 'clinician-preferred' ventilation strategy.

6.4.4.2. Observed unit-specific patterns of ventilatory strategy

Where possible, identifiable ventilatory strategies (i.e. those identified in 6.7.3) that are nested within an ICU, will be evaluated within a model that stratifies by status with respect to suspected or proven pandemic infection, where appropriate within a Bayesian Hierarchical Model that takes into account unit and country level effects.

6.4.4.3. Observed individual patient patterns of ventilatory strategy

Where possible, identifiable ventilatory strategies (i.e. those identified in 6.7.3) will be evaluated in a model, without recourse to nesting of the strategy within an ICU.

6.4.4.4. Individual patient observational analysis

Observational analyses may be conducted that report association between ventilator parameters and outcome, taking into account, where possible, potential effect modifiers (i.e. with or without suspected or proven COVID acute respiratory failure) as well as confounding (noting that variables that contribute to confounding are potentially dynamic).

6.4.5. Principles of analysis

In the preliminary phase of this domain a fixed sample size will be chosen, after which, analysis will be conducted with presentation and publication of the results. Subsequent adaptations would then be planned, on the basis of publicly available results, and, where appropriate, data collected from patients enrolled in the preliminary phase may be used in analysis or used to generate priors in ongoing models. Where appropriate, Bayesian Hierarchical Models may be used to capture the treatment effect of different modifiable components of ventilatory strategy.

This domain complies with the requirements of the core protocol documents. Although no simulations will be conducted, this is appropriate because the only element of the design that is pre-specified is the preliminary nature of this phase and the fixed sample size. As such, and to achieve the objectives of the preliminary phase, it is not necessary to undertake simulations to understand the risks of type I and type II error.

6.5. *Summary of background*

Severe non-COVID CAP and COVID acute respiratory failure which requires mechanical ventilation is associated with significant morbidity and mortality. CAP commonly requires invasive mechanical ventilation. This ventilation has the ability to further damage the injured lung. While international guidelines offer some principles for care of these patients, many of these recommendations rely either on weak evidence or on extrapolation of data from patients with ARDS which may not be justified for all patients with non-COVID CAP or acute respiratory failure due to COVID. There is substantial uncertainty regarding optimal ventilation strategy. Possibly because of this uncertainty, clinicians adhere poorly to these recommendations.

The preliminary phase of the ventilation domain will randomize patients to either clinician-preferred or protocolized therapy with the information obtained from this phase being utilized to design subsequent phases of the ventilation domain including setting entry criteria, determining interventions, and setting strata that may be associated with differential treatment effect.

7. DOMAIN OBJECTIVES

The long-term objective of this domain is to determine the most effective mechanical ventilation strategies for the treatment of patients with severe CAP and COVID-19 pneumonia who are receiving invasive mechanical ventilation.

The objectives of the initial phase of the domain are, from a fixed sample size, to:

1. Collect physiological and ventilatory data on invasively ventilated patients enrolled into the REMAP-CAP trial.
2. Evaluate separation between protocolized and clinician-preferred mechanical ventilation.
3. Evaluate adherence with protocolized mechanical ventilation in patients with and without suspected and proven COVID-19 acute respiratory failure.
4. Compare outcome between patients allocated to receive protocolized mechanical ventilation with patients treated with clinician-preference mechanical ventilation including evaluation of potential differential treatment effect across strata defined by status with respect to whether pandemic infection is suspected or proven and across ordinal stratum of PaO_2:FiO_2 ratio
5. Identify patterns of clinician-preferred mechanical ventilation that can be analyzed as an 'intervention group' within the initial phase or potentially deliverable as intervention in subsequent phases or both
6. Compare outcome in patients with different 'intervention groups' within clinician-preferred mechanical ventilation using protocolized mechanical ventilation as the common comparator group across evaluable strata
7. Identify variables that may influence treatment effect for different ventilatory strategies that may be used as strata variables in subsequent phases
8. Utilize information and analysis to revise the protocol design and pre-specified adaptations of the mechanical ventilation domain in subsequent phases

We hypothesize that the probability of all-cause mortality at 90 days after enrollment will differ based on the mechanical ventilation strategies treatment received. This preliminary phase will likely be underpowered to demonstrate superiority. However, it is necessary for the planning of the subsequent phase. The current mechanical ventilation strategies that will be available to be tested are:

- Protocolized mechanical ventilation
- Clinician-preferred mechanical ventilation

There are multiple other hypotheses, but these are all regarded as preliminary and hypothesis generating. These hypotheses are that:

- Within the clinician-preferred ventilation strategy, that 90-day mortality differs depending on definable patterns of ventilatory strategy

- There is interaction between allocation status and outcome depending on strata (PaO_2:FiO_2 ratio and pandemic infection strata status), lung compliance, and unilateral v bilateral lung disease (i.e. infiltrates) at baseline

The long-term objective of the domain is to identify optimal ventilatory strategy and how this varies between patients with different definable baseline characteristics and how this varies over time and progression of lung disease. The goals of the preliminary phase are:

- Define testable and deliverable ventilatory strategies that can be introduced as interventions in subsequent phases of the domain
- Identify baseline stratification variables that can be utilized to allow evaluation of potential differential treatment effect and be used for implementation of response adaptive randomization (RAR)
- Adapt the domain, taking these factors into account

8. TRIAL DESIGN

8.1. *Trial design overview*

This domain will be conducted as part of a REMAP trial for severe CAP (see relevant core documents). Treatment allocation will not be adaptive during the preliminary phase. This domain is designed so that it could be supplemented by enrolment of patients with respiratory failure due to causes other than CAP, but this is not a feature of the current design.

Although this domain is conducted as part of REMAP-CAP, it will use a statistical model that is separate to the other domains of REMAP-CAP. The strata that apply to this domain are pandemic infection status and PaO_2:FiO_2 ratio but, with respect to PaO_2:FiO_2 the strata that are applied in this domain are a sub-set of states that are defined in the relevant core protocol documents, but they are applied as strata, at the time of randomization or reveal of allocation assignment.

8.2. *Population*

The REMAP enrolls patients with severe CAP admitted to ICU and patients with acute illness due to suspected or proven COVID-19 admitted to ICU.

8.3. *Eligibility criteria*

Patients are eligible for this domain if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria as specified in either the REMAP-CAP Core Protocol +/- Pandemic Appendix or the REMAP-COVID Core Protocol. Patients otherwise eligible for REMAP-CAP may have conditions that exclude them from the Mechanical Ventilation Domain.

8.3.1. Domain inclusion criteria

Patients will be included in this domain if the have the following:

- Receiving invasive mechanical ventilation
- The most recent PaO_2:FiO_2 ratio obtained within the preceding 6 hours is less than 200 mmHg
- Treating clinician expects the patient to still require invasive mechanical ventilation tomorrow.
- Treating clinician regards Protocolized Mechanical Ventilation Strategy or their preferred mode as (equally) appropriate for this patient.

8.3.2. Domain exclusion criteria

Patients will be excluded from this domain if they have any of the following:

- More than 48 hours has elapsed since commencement of invasive mechanical ventilation
- The treating clinician believes that participation in this domain is not in the best interests of the patient.

8.4. *Interventions*

8.4.1. Mechanical Ventilation Interventions

Patients will be randomly assigned to receive one of the following open-label study interventions.

- Protocolized mechanical ventilation
- Clinician-preference mechanical ventilation

8.4.2. Physiological targets set prior to reveal of allocation status and common to both interventions

In the event of an oxygen saturation target domain of REMAP-CAP, this target would be allocated by randomization within this domain for patients who receive an allocation status in the oxygen saturation target domain. In the absence of an oxygen saturation target domain, at the time of establishing eligibility, the treating clinician will specify a current target range for the oxygen

saturation. This may be provided as a component of the allocation status for the patient but is determined by the treating clinician and can be adjusted at any time by the treating clinician.

At the time of establishing eligibility, the treating clinician will specify a target range for the arterial $PaCO_2$. This may be provided as a component of the allocation status for the patient but is determined by the treating clinician and can be adjusted at any time by the treating clinician.

8.4.3. Clinician-preferred mechanical ventilation strategy

The clinician will choose the mode of ventilation and all ventilatory parameters that they would use normally for this patient. Acceptable modes of ventilation include but are not limited to Pressure Control, synchronised intermittent mandatory ventilation (SIMV), Assist Control (AC), and APRV. Any and all ventilatory parameters, including mode of ventilation, can be adjusted at any time. If the treating clinician would usually apply low tidal volume ventilation this is acceptable.

Sedative medications should be administered, as determined by the treating clinician, with or without administration of a neuromuscular blocker, to provide patient safety and comfort as well as to allow delivery of the specified ventilator settings.

Each participating ICU will be asked to outline the mechanical ventilation strategy that is used most commonly, and this may be made available to guide patient care but is regarded only as advisory and deviation from this guide is permitted at any time.

8.4.4. Protocolized mechanical ventilation strategy

At the time of establishing eligibility, if feasible, the patient's height will be entered into the on-line eligibility system which will be used to calculate PBW and to specify a starting tidal volume that will be set on the ventilator that corresponds to a tidal volume of 6.0 ml/kg PBW. The treating clinician will set the mode of ventilation as either SIMV, Assist Control, or pressure regulated volume control, setting the tidal volume to that specified by the on-line eligibility system or calculated by the site. If the plateau pressure is more than 30 cmH_2O, the tidal volume should be reduced in 5 to 10% increments, but to not less than 65% of the initial specified tidal volume (corresponding to 4.0 ml/kg PBW). At any time, if the tidal volume is less than that specified following calculation from the patient's height and the plateau pressure is 29 cm or less, the tidal volume should be increased in 5% increments to achieve a tidal volume as close to, but not exceeding, the specified target tidal volume while maintain plateau pressure of not more than 30 cm H_2O.

The respiratory rate is set by the treating clinician with the goal of achieving the targeted $PaCO_2$ and adjusted, as required, to achieve the $PaCO_2$ target. If the $PaCO_2$ target cannot be achieved the respiratory rate should be adjusted upwards preserving, at all times (unless pH of arterial blood is less than 7.15 see below), the tidal volume (and plateau pressure target). The maximum rate is 35 breaths per minute.

Sedative medications should be administered, as determined by the treating clinician, with or without administration of a neuromuscular blocker, to provide patient safety and comfort as well as to allow delivery of the specified ventilator settings.

If arterial pH is less than 7.15, the tidal volume can be increased in 5 to 10% increments until arterial pH is more than 7.15, noting that, if necessary, to maintain a pH of not less than 7.15, it is permitted for the plateau pressure to exceed 30 cm H_2O. In the presence of severe acidosis, bicarbonate may be administered, at the discretion of the treating clinician. If the acidosis has a substantial metabolic component, continuous renal replacement therapy may be instituted, at the discretion of the treating clinician.

Administration of a tidal volume of more than 6.0 ml/kg PBW or a plateau pressure of 30 cm H20 or more is a protocol deviation unless the pH is less than 7.15.

The FiO_2 and PEEP should be set on the ventilator to the minimum allowable combination of FiO_2 and PEEP that consistently achieves a PaO_2 / SaO_2 within the target range and adjusted further, as required according to either of the tables below which is derived from either the ARMA ARDSnet trial (the standard PEEP arm) OR the LOVS and ALVEOLI trials (the high PEEP arm) (Meade et al., 2008, Brower et al., 2004). Given that the original ARDSnet including the standard PEEP arm is frequently the control group in ventilation studies and many units still deliver the original ARDS net protocol (including the standard PEEP approach), we will allow units to use either FiO_2 / PEEP table below. Each participating Intensive Care Unit will declare *a priori* which PEEP table it will follow in the Protocolized intervention.

The ARDSnet PEEP (standard PEEP) strategy

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 (cm H_2O)	5	5	8	8	10	10	10	12	14	14	14	16	18	18-24

Or the LOVS / ALVEOLI (High PEEP) strategy

F_iO_2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
PEEP (cmH_2O)	5 to 14	10 to 18	16 to 20	20	20	20 to 22	22	22-24

If the patient has a significant and sudden drop in saturation, it is permitted to increase the PEEP/FiO_2 rapidly from the left to the right of the chart as quickly as required to achieve an oxygen saturation that is in the target range. If there is doubt about accuracy of a SaO_2, arterial blood gases should be measured and used to adjust the PEEP and FiO_2 as required.

The delivery of protocolized mechanical ventilation will be facilitated by training of site personnel, the availability of bedside study tools, and audit and feedback to sites regarding adherence to the protocol. The use of any other mode of controlled mechanical ventilation (pressure control, APRV) is a protocol deviation. Administration of a combination of PEEP and FiO_2 that is not specified by the table is a protocol deviation unless the plateau pressure is 30 cm of H_2O or more.

8.4.5. Duration of administration of domain intervention.

The duration of administration of the interventions outlined in this domain is at the discretion of the treating clinician. The entry criteria of the domain are designed to identify patients who are likely to require ventilation for at least 24 hours. Adherence to the allocated treatment should continue as long as the patient is receiving invasive ventilation or until day 28, whichever occurs first. The introduction and transition to spontaneous ventilation is at the discretion of the treating clinician. Criteria for readiness for a trial of unsupported or minimally supported spontaneous ventilation are not specified by the trial and are at the discretion of the treating clinician. Criteria for extubation, or insertion of a tracheostomy tube, are not specified by the trial and are at the discretion of the treating clinician.

8.5. *Concomitant care*

All other interventions will be as directed by the treating clinician, including choice of sedative agents, depth of sedation, use of neuromuscular blocking agents, and use of rescue therapies for severe hypoxemia including prone positioning, inhaled pulmonary vasodilators, ECMO, and $ECCO_2R$, although the use of these therapies will be recorded.

8.6. *Endpoints*

8.6.1. Primary endpoint

The primary endpoint for this domain is all-cause mortality at 90 days.

8.6.2. Secondary endpoints

All secondary endpoints as specified in the REMAP-CAP Core Protocol +/- Pandemic Appendix or REMAP-COVID Core Protocol.

The domain-specific secondary outcome measures (occurring during the index hospitalization, censored 90 days after enrollment) are:

- Administration of rescue therapies
- Occurrence of barotrauma
- SAE as defined in the core protocol documents and qualified in this DSA

8.6.3. Process end-points

Ventilator settings, targets for oxygen saturation and arterial $PaCO_2$, and corresponding results of arterial blood gases will be recorded. Qualitative and quantitative assessment of factor influencing threshold for equipoise for randomization, choice of preferred strategy, and barriers to adherence.

9. TRIAL CONDUCT

9.1. *Domain-specific data collection*

9.1.1. Clinical data collection

Additional domain-specific data will be collected.

- Baseline ventilatory, physiological parameters and arterial blood gas parameters
- Daily ventilatory and physiological parameters and arterial blood gas parameters

- Daily targets for physiological parameters, if specified
- Occurrence and duration of prone ventilation.
- Administration of rescue therapies
- Occurrence of barotrauma

9.2. *Criteria for discontinuation*

Refer to relevant core protocol documents for criteria for discontinuation of participation in the REMAP-CAP trial.

9.3. *Blinding*

9.3.1. Blinding

The interventions in the ventilation domain are not suitable for blinding as the appropriate care of the patient requires the clinician to have knowledge of the ventilator settings.

9.3.2. Unblinding

Not relevant.

10. STATISTICAL CONSIDERATIONS

10.1. *Domain-specific stopping rules*

The domain can report a Platform Conclusion, as specified in relevant Core Protocol, at any interim analysis. The possible Platform Conclusions are superiority (with corresponding inferiority) of either intervention. The Platform Conclusion of equivalence will not be evaluated during the preliminary phase.

In the absence of a Platform Conclusion, the domain will be analyzed after 400 patients have been enrolled, although randomization using this version of the protocol will continue beyond 400 patients while results from the initial phase are being analyzed which will be used to guide subsequent adaptations to the domain.

10.2. *Categorization of clinician-preferred ventilator strategies*

10.2.1. Unit-level self-categorization

As part of the site initiation process, the opinion of clinicians at that site will be obtained regarding their usual approaches to ventilation including whether there is a belief that guideline-recommended ventilation is utilized and, if so, for what category of patients. If guideline-recommended ventilation is not utilized the common patterns of ventilatory strategy will be identified. Patterns of ventilatory strategy that are common between sites will be identified and sites will be categorized according to shared patterns of ventilatory strategy.

10.2.2. Unit-level observed categorization

Data obtained from non-randomized and randomized patients will be analyzed to identify common patterns of ventilatory strategy in CAP and patients with proven or suspected COVID-19. Patterns of ventilatory strategy that are common between sites will be identified and sites will be categorized according to shared patterns of ventilatory strategy.

10.2.3. Patient-level categorization

Data obtained from individual non-randomized and randomized patients will be analyzed to identify common patterns of ventilatory strategy. Patterns of ventilatory strategy that are common among all patients, irrespective of participating site, will be identified and patients will be categorized according to shared patterns of ventilatory strategy.

10.2.4. Methods of determination of categorization

Conventional statistical methods will be applied to identify categories such as classification and regression trees (CART) and logistic regression. If available to the investigators, additional methods such as network analysis may be used.

10.3. *Statistical analysis*

10.3.1. Principles of statistical analysis

The statistical analysis of the ventilation domain will follow the principles outlined in the relevant core protocol documents with some modifications, as outlined in this DSA.

Treatment effects will be evaluated in this domain using a statistical model that is separate to the model used for other domains of REMAP-CAP. The model will be specified and described in an

operational document that may be updated periodically. The model will estimate the probability of superiority, after adjustment for baseline covariates, dependent on allocation status to clinician preferred or guideline recommended ventilation strategy. Equivalence will not be evaluated during the initial phase. The statistical model will include stratification by the pandemic infection stratum with borrowing permitted between stratum. Randomization occurs at the time of reveal, i.e. not necessarily at the time of first assignment in any domain. This allows for the application of strata that apply at the time of randomization. The additional strata will comprise ordinal categories of PaO_2:FiO_2 ratio with borrowing permitted across ordinal stratum categories. The use of Statistical Triggers and Platform Conclusions will be as specified in the core protocol documents. The sample size for the initial phase will be a maximum of 400 patients who have been randomized.

The same or similar model, if appropriate in conjunction with a Bayesian Hierarchical Model, will be used to evaluate the effect of identified ventilatory strategies. In these analyses, patients within the clinician-preferred strategy will be analyzed according to groups that identify specific ventilatory strategies with analysis being applied at both site level (site self-reported strategy and site observed strategy) and patient level. If appropriate, a BHM may be used that takes into account the relationships between patient- and site-level categorization of ventilatory strategies and evaluates the impact of ventilatory parameters, as well as progression of the underlying disease and alternative strata. Sensitivity analyses using data from non-randomized may also be conducted.

10.3.2. Strata

The strata structure of this domain comprises the 2 x 3 table defined by two categories of the pandemic infection strata combined with 3 ordinal categories defined by the PaO_2:FiO_2 ratio at time of randomization (noting that in this domain, randomization occurs at the time of reveal which is different to the other domains of REMAP-CAP). The ordinal strata are:

- PaO_2:FiO_2 ratio less than 100
- PaO_2:FiO_2 ratio of 100 or more but less than 150
- PaO_2:FiO_2 ratio of 150 or more but less than 200

These categories are a sub-set of state, as defined in core protocol documents.

10.3.3. Primary analysis

The primary analysis will evaluate the main effect of assignment to either clinician-preferred or protocolized ventilatory strategy. Each stratum is analyzed separately but the model captures commonalities across stratum, recognizing the ordinal structure of the strata. Additionally, the

statistical model allows evidence relating to the effectiveness of a ventilatory strategy in one stratum to contribute (via 'borrowing') to the estimation of the posterior probability in other stratum, but this only occurs to the extent that treatment effect is similar in adjacent stratum. The model will adjust for demographic and severity factors but will not provide a separate estimate of treatment effect for these covariates.

The primary analysis set will comprise patients who receive an allocation status, i.e. intention to treat. Additional analyses may be undertaken on a per protocol basis (i.e. taking into account adherence with guidelines) and utilizing data from non-randomized patients.

10.3.4. Descriptive analysis of ventilatory patterns

Conventional parametric or non-parametric, as appropriate, statistical methods will be used to describe observed ventilator settings including mode of ventilation, tidal volume, airway pressures, PEEP, saturation target and its achievement, $PaCO_2$ target and its achievement.

10.3.5. Secondary analyses

A series of secondary analyses will be conducted. Higher emphasis will be given to results that are consistent across multiple different analyses.

10.3.5.1. Evaluation of adherence with protocolized ventilatory strategy

Adherence with protocolized ventilatory strategy will be evaluated by the duration for which the strategy is implemented as a proportion of the total time the patient receives a mandatory ventilation mode, censored at day 28; and by the proportion of tidal volume and PEEP measurements that are compliant with the treatment protocol during the period of time for which the strategy is implemented. Factors associated with adherence will be evaluated using logistic regression utilizing variables include, but are not limited to age, co-morbidity (including chronic obstructive pulmonary disease, COPD), pattern of lung involvement (unilateral CAP, bilateral CAP without moderate / severe ARDS, or moderate / severe ARDS), lung compliance, PaO_2:FiO_2 ratio stratum, pandemic infection stratum, and participating site. The analysis set will comprise patients assigned to protocolized ventilatory strategy.

10.3.5.2. Identification of patterns of clinician-preferred mechanical ventilation that can be analyzed as an intervention group

Each participating ICU will be asked, using self-report, to identify commonly applied ventilatory strategies. This will comprise information related to mode of ventilation; targets with respect to one or more of tidal volume, plateau pressure, oxygen saturation, and $PaCO_2$; use of APRV, and timing of

switching to spontaneous ventilation. Qualitative thematic analysis of this information will be used to identify candidate ventilatory strategies which may be mutually exclusive or overlapping.

Several methods will be used to identify common patterns of ventilatory strategy. These include the extent to which observed ventilatory patterns correspond to the candidate ventilatory strategies identified by analysis of self-reported strategies, CART or logistic regression-based methods, and network analysis which identifies commonalities across all recorded parameters and organizes these into nodes of similarity.

The analysis set will be patients randomized to clinician-preferred strategy.

Identified ventilatory strategies will also be evaluated by investigators to determine the extent that such strategies could be specified for delivery using a protocol.

10.3.5.3. Evaluation of treatment effect associated with identified patterns of ventilatory strategy

A Bayesian statistical model will evaluate the treatment effect of different identified patterns of ventilatory strategy, from among patients assigned to clinician-preferred ventilatory strategy, using protocolized ventilation as the common comparator. The model will be similar or the same as that uses for the primary analysis. If appropriate, a hierarchical structure may be utilized that groups together elements of identified strategy that are similar for example APRV and among non-APRV patients pressure control versus volume control (and whether tidal volume or inspiratory pressure is targeted), and the use of PEEP. Analyses will also be conducted in which the unit of analysis is categories of participating ICU according to self-reported ventilatory strategy as well as observed ventilatory strategy. The analysis will be conducted using the pandemic infection strata and ordinal PaO_2:FiO_2 strata, and take into account the same baseline co-variates.

The analysis set will be all randomized patients.

10.3.6. Identification of variables that may modify treatment effect

An important component of the initial phase is the identification of strata variables for subsequent phases. Although PaO_2:FiO_2 ratio has been selected as the strata variable for the initial stage it is possible that other variables, alone, or in combination with PaO_2:FiO_2 ratio, may have greater potential to identify patient characteristics associated with differential treatment effect. The potential for alternative variables to be used for stratification will be evaluated using a Bayesian statistical model that evaluates differential treatment effect according to baseline variables including age, co-morbidity

(including COPD), pattern of lung involvement (unilateral CAP, bilateral CAP without moderate / severe ARDS or moderate / severe ARDS), and lung compliance on treatment effect for the assigned ventilatory strategies, as well as identified ventilatory patterns among patients allocated to receive clinician-preferred ventilation.

10.3.7. Evaluation of separation between protocolized and clinician-preferred ventilatory strategies

Conventional statistical methods will be used to evaluate separation with regard to ventilatory parameters including but not limited to mode of ventilation, tidal volume, inspiratory pressures, PEEP, and initiation of spontaneous ventilation. Logistic regression methods will be used to identify factors associated with separation. Variables that will be evaluated include, but are not limited to, age, co-morbidity (including COPD), pattern of lung involvement (unilateral CAP, bilateral CAP without ARDS, ARDS), lung compliance, stratum, and participating site.

10.3.8. Sample size and statistical power

This initial phase is conducted as part of an ongoing platform, as outlined in the core protocol documents. There is little rationale for pre-specification of the size of expected treatment effects and, as such, it is difficult to specify the statistical power that is available for the primary analysis. It is anticipated that only a large treatment effect would be capable of detection with a sample size of 400 patients. The statistical power available for evaluation of identified variants of clinician-preferred ventilation is commensurately smaller.

The primary objective of the initial phase is to redesign the domain utilizing the generated data. If data from 400 patients is insufficient for this purpose, the initial phase can be extended. The sample size of 400 patients was chosen based on expected rates of recruitment and a compromise between the need for data to design subsequent phases and the time imperative to move as quickly as possible from the initial to subsequent phases. In this regard, the initial phase can be regarded as a pilot study.

10.4. *Timing of revealing of randomization status*

The timing of the revealing of allocation status and administration of interventions is as specified to be Randomization with Immediate Reveal and Initiation.

10.5. *Interactions with interventions in other domains*

No interaction with other domains is capable of being evaluated because of the use of a separate statistical model for the ventilation domain.

10.6. *Nesting of interventions*

Nesting is not applicable to this domain.

11.ETHICAL CONSIDERATIONS

11.1. *Data Safety and Monitoring Board*

The DSMB should be aware that the superiority, inferiority, or equivalence of different interventions with respect to the primary endpoint is possible and will interpret adaptive analyses accordingly and aware of the objectives of this initial phase of the ventilation domain.

11.2. *Potential domain-specific adverse events*

Potential domain-specific harms related to the ventilation domain include:

- Barotrauma (i.e. pneumothorax, subcutaneous emphysema, etc.)

Other serious adverse events (SAEs) should be reported only where, in the opinion of the site investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see relevant core protocol documents).

11.3. *Domain-specific consent issues*

All patients eligible for this domain will not be competent to consent because of administration of sedative agents to facilitate invasive mechanical ventilation. All ventilatory strategies are within the spectrum of standard care at participating ICUs. The treatment options are either what is recommended by international guidelines or the treatment the patient would have otherwise received. Randomization is precluded if the treating clinician believes that participation is not in the best interests of the participant. On this basis, where available, it is proposed that enrollment will occur without prior agreement, with agreement being obtained from a patient representative or the patient or both as soon as possible.

During a pandemic, visiting by relatives of affected patients may not be possible. In such situations, alternative methods for confirming consent including electronic and telephone communication, as permitted by an appropriate ethical review body, may be acceptable methods of confirming agreement to participate in this (and other) domains of the platform.

Clinicians are directed not to enroll an individual patient if the treating clinician believes that participation in this domain is not in the best interests of the patient.

12.GOVERNANCE ISSUES

12.1. *Funding of domain*

Funding sources for the REMAP-CAP trial are specified in the core protocol documents. This domain has not received any additional domain-specific funding but such funding may be obtained during the lifetime of the domain.

12.2. *Funding of domain interventions and outcome measures*

All patients will require mechanical ventilation. There are no additional costs for setting of ventilatory parameters that are available on all ventilators at participating sites.

12.3. *Domain-specific declarations of interest*

All investigators involved in REMAP-CAP maintain a registry of interests on the REMAP-CAP website. These are updated periodically and publicly accessible on the study website.

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APPENDIX 1.

1. LUNG PATHOLOGY IN CAP

CAP can be caused by infection with a variety of different microorganisms, including those with pandemic potential (i.e. COVID-19) but irrespective of the specific microbiological cause it is marked by major changes in the alveoli of the lungs where gas exchange occurs (Marrie, 1998). There is infiltration of inflammatory cells and loss of capillary permeability, leading to leakage of fluid, both of which result in the filling of the alveoli so that gas is unable to enter or leave the alveoli, thus impairing transfer of oxygen and carbon dioxide.

Two broad patterns of CAP pathology are recognized- lobar pneumonia and bronchopneumonia. Lobar pneumonia occurs when one or more lobes of the lung are affected, and can be bilateral, whereas bronchopneumonia is more widespread, often bilateral, and does not follow a clear lobar pattern. CAP caused by viruses, such as COVID-19 and influenza, tends to be diffuse (bronchopneumonia pattern) whereas bacterial infection can result in either pattern (Lei et al., 2020).

The Acute Respiratory Distress Syndrome (ARDS) is an inflammatory lung disease characterized by acute onset, bilateral lung opacities on radiological imaging, and respiratory failure with impaired transfer of oxygen that is not caused by heart failure or volume overload (Force et al., 2012). There are many different causes of ARDS, but CAP is leading cause. Most mechanical ventilation trials have enrolled patients with ARDS, a substantial proportion of whom will have had CAP as the cause of their ARDS. As such, many of the strategies utilized in patients with CAP are derived from trials of patients with ARDS, even if the patient does not have ARDS. The relevance of this is uncertain, but the situation of greatest likelihood of relevance is in patients with unilateral pneumonia in whom the function of the unaffected lung is normal or only mildly abnormal. Interestingly, in COVID-19 acute respiratory failure, while the CXR findings are consistent with ARDS, CT findings are not the classical ARDS appearance, suggesting that the extrapolation of ARDS ventilation strategies for all COVID-19 patients might not be appropriate (Lei et al., 2020, Li et al., 2020, Bao et al., 2020, Goodman, 2000).

In addition to CAP and ARDS, per se, mechanical ventilation is known to be capable of causing lung damage - so called Ventilator Associated Lung Injury (VALI) (Rocco et al., 2012). This damage can be secondary to excessive volumes or pressures applied to the lung or by repetitive opening and closing of collapsed alveoli. *Volutrauma* refers to alveolar damage secondary to excessive tidal volume breaths delivered by the mechanical ventilation. *Barotrauma* refers to alveolar damage secondary to excessive pressures delivered by mechanical ventilation. *Atelectatrauma* is alveolar damage

secondary to collapsed alveoli cyclically opening and closing with each mechanical ventilation breath. Mechanical ventilation strategies have aimed to minimize these injurious effects on the already damaged lung. This is particularly important as the pathway to death in some patients with CAP or ARDS or both is Multi-Organ Dysfunction Syndrome (MODS) and not from severe hypoxemia. There is evidence that inflammation in the lungs, *biotrauma*, produces inflammatory mediators that contribute to failure of other organ systems.

The natural history of CAP in survivors, as well as ARDS and lung damage from mechanical ventilation, is for improvement to occur over time. With respect to CAP, antimicrobial treatment, in combination with the patient's own immune response, results in clearance of infection and resolution of inflammation. A subset of patients with ARDS can develop a condition known as fibroproliferative ARDS in which lung fibrosis develops which can resolve slowly although it can also result in permanent lung damage. Nevertheless, most patients with CAP who survive will recover to have normal or near-normal lung function (Lamping et al., 2002).

2. PHYSIOLOGICAL PRINCIPLES AND OPTIONS AVAILABLE IN SETTING VENTILATORY STRATEGY

2.1. *Introduction*

Invasive mechanical ventilation delivers breaths into the lungs during inspiration. Expiration is a passive process, resulting from the elastic recoil of the lungs and chest wall. There are three features that characterize invasive mechanical ventilation- how the characteristics of the inspiratory breath are determined, the application of pressure during expiration which is referred to as positive end-expiratory pressure (PEEP), and whether breaths are mandatory or triggered. Mandatory breaths are fully initiated by the ventilator whereas triggered breaths support a respiratory effort initiated by the patient that is sensed by the ventilator. At any given time, a ventilator can deliver a ventilation strategy that comprises only mandatory breaths or only triggered breaths or a combination of mandatory and triggered breaths.

In the following sections, each of these components of ventilation is described. Further sections describe methods that are applied by the ventilator to minimize VILI, other methods used with the intention of improving lung function, the process of weaning and separation from invasive mechanical ventilation, and an explanation for the role of administration of sedative agents and neuromuscular blocking agents. This section outlines principles that relate predominantly to physiology and does not

include a description of evidence from trials or observational studies regarding the impact of these factors on outcome.

2.2. *Lung physiology during invasive mechanical ventilation*

In its simplest form, mechanical ventilation provides breaths to the patient, these are best described as tidal volume (the size of the breath delivered (mis)) and the rate that these breaths are delivered (respiratory rate-breaths per minute). The respiratory rate times the tidal volume gives the minute ventilation for that patient (mis/min). When a tidal volume breath is delivered to a patient this provides alveolar ventilation. The pressure needed to deliver this tidal volume breath is determined by the resistance and compliance of the respiratory system. Static respiratory compliance is commonly measured by clinicians, as a measure of lung disease. Over the last 40 years it has become clear that the application of a positive pressure at the end of a delivered breath (PEEP, positive end expiratory pressure) prevents the collapse of alveoli during mechanical ventilation.

2.3. *Pressure or volume during inspiration*

For mandatory breaths, there are two options available to the treating clinician that determine the size of mandatory breaths, either application of specified pressure for the duration of inspiration (which is also specified by the treating clinician) or delivery of a specified volume that occurs over a duration of inspiration (which is also specified). For the purposes of this document, the former is referred to as Pressure Control ventilation and the latter as Volume Control ventilation. With Pressure Control ventilation, the positive pressure that is applied during inspiration is set by the treating clinician but the volume of gas that is delivered each breath is dependent on the compliance characteristics of the lung and chest wall and, because the compliance characteristics in diseased lungs are dynamic, so the delivered tidal volume can also change. With Volume Control ventilation, the tidal volume is set by the treating clinician but the airway pressure that occurs can vary, as a consequence of changes in the compliance characteristics. Irrespective of whether a clinician chooses to use Pressure Control or Volume Control ventilation, the clinician must choose settings and be aware of the potential consequences of changes in compliance characteristics. Decisions regarding the prescribed pressure or volume will influence minute volume and there is a relationship between minute volume, and hence the selected pressure or volume, and clearance of carbon dioxide and the level of carbon dioxide in arterial blood ($PaCO_2$).

2.4. *Characteristics of inspiration and ventilator induced lung injury*

It is believed that there is a relationship between the size of tidal volume or the applied pressure or both that results in damage to the lung (Rocco et al., 2012). During mechanical ventilation, inspiration is the process whereby the mechanical ventilator drives gas over an amount of time into the patient's lungs. Choices that the treating clinician makes influences the volume, the time, the maximal pressure, the rate and the pattern of this delivery. These are active processes that require energy.

It is known that higher tidal volumes and higher pressures delivered by the mechanical ventilator can damage both healthy and already injured lungs (Rocco et al., 2012). This damage can be microscopic, volutrauma and barotrauma; macroscopic, such a pneumothorax, pneumomediastinum; or functional due to the expanding lungs compressing other intrathoracic organs, such as the great vessels and the heart but the constant feature across all of these forms of damage is that there is a relationship between the size of breath and injury (Acute Respiratory Distress Syndrome et al., 2000, Walkey et al., 2017).

2.5. *Expiration and PEEP*

As indicated, expiration is a passive process, relying on the elastic recoil of the lungs and chest wall. During conventional invasive mechanical ventilation, the duration of expiration is typically longer than the duration of inspiration. In some ventilatory strategies the duration of expiration is set on the ventilator by the treating clinician while in others the pattern of the patient's own breathing influences the duration of expiration.

PEEP is the pressure maintained by the mechanical ventilator after expiration and during invasive mechanical ventilation and it is usual practice to apply an amount of PEEP. During invasive mechanical ventilation PEEP serves to promote resolution of areas of collapse and open alveoli that are filled with edema fluid. There is a relationship between mean airway pressure and effectiveness of oxygen transfer, and, so, progressive increases in the amount of PEEP is used commonly as a strategy in an attempt to improve transfer of oxygen in patients with progressive impairment of oxygen transfer. The usual range of PEEP lies between 5 cm H_20 (water) and 25 cm H_20. Higher PEEP however can contribute to the risks of barotrauma and may impair right heart function, reducing cardiac output and blood pressure.

In addition to fractional inspired oxygen concentration (F_iO_2), PEEP, in combination with mean airway pressure, are determinants of transfer of oxygen from inhaled gas into arterial blood. Higher levels of PEEP are used to improve gas exchange in damaged lungs. However, it is also recognized that PEEP

may also attenuate VILI. This protective effect of PEEP may be due to splinting open of previously collapsed alveoli and preventing the repetitive opening and closing of these alveoli (reducing atelectotrauma) or by opening previously closed alveoli that can now participate in ventilation and help accommodate a tidal breath (reducing volutrauma and barotrauma).

2.6. *Mandatory and triggered breaths*

With invasive mechanical ventilation, there are two ways in which any given breath can be initiated. The term mandatory breath applies when the clinician specifies that a certain number of breaths must be delivered by the ventilator per minute. The term triggered breath applies when the ventilator is able to sense that the patient has made an inspiratory effort and then support that breath with application of additional positive pressure (termed Pressure Support) Invasive mechanical ventilation can be fully mandatory (no triggered breaths), fully triggered (no mandatory breaths), or a combination of the two.

2.7. *Airway Pressure Release Ventilation (APRV)*

APRV is a mode of ventilation that is qualitatively different from conventional Pressure Control or Volume Control ventilation (Carsetti et al., 2019). APRV is a pressure-limited, time-cycled mode of ventilation that allows unrestricted spontaneous breathing throughout the respiratory cycle. The APRV respiratory cycle comprises a prolonged period of continuous positive airway pressure termed P_{High} that is usually between 80-95% of the cycle time. This is followed by a short time-cycled release phase, termed T_{Low}, (usually 0.2-0.8 seconds), to a lower pressure termed P_{low}. P_{low} is usually set at zero cmH2O. The T_{Low} release phase is explicitly set to terminate prior to flow dissipation in order to induce a degree of gas trapping thereby maintaining a degree of positive end-expiratory pressure and volume.

A number of potential mechanisms that may result in advantage of APRV compared to other conventional modes of ventilation have been proposed. These include increasing the surface area available for gas exchange by maximizing time-dependent alveolar opening during the sustained P_{High} phase, enhanced recruitment of dependent lung regions as a result of negative pleural pressure generated by spontaneous breaths, improving CO_2 removal through the use of an expiratory 'release' phase, reduction in the pressure or energy required to inflate alveolar units by avoiding the airway impedance and elastic forces associated with overcoming lower baseline resting lung volumes, and improved cough and secretion clearance through a reduction in depth of sedation and avoidance of

neuromuscular blockade as a consequence of the goal of facilitating unrestricted spontaneous breathing throughout the respiratory cycle.

2.8. *Recruitment maneuvers*

Recruitment maneuvers involve the temporary application of high pressures to the airways in an attempt to open previously collapsed alveoli (Gattinoni et al., 2006). The pressures used with 'safe' conventional mechanical ventilation (<30-35cm H_20) are frequently insufficient to open the majority of the collapsed alveoli in ARDS / severe CAP. These maneuvers can be static (i.e. application of Continuous Positive Airway Pressure (CPAP) to 40cm H_20 for 40 seconds) or dynamic (i.e. stepwise recruitment where PEEP is increased incrementally in 10 cm H_20 steps from 20 cmH_20 to 40 cmH_20 while ventilation is ongoing). There have been concerns that the higher airway pressures used, even transiently, may increase the risk of barotrauma and may impair right heart function (Goligher et al., 2017).

It has been recently recognized that not all patients with ARDS respond (i.e. improved oxygenation or lung compliance) to a recruitment maneuver. Some patients labelled 'responders' have dramatic increases in recruited lung and may accrue benefits due to reduced volutrauma, barotrauma and atelectotrauma with ongoing mechanical ventilation. However, others, labeled non-responders (i.e. no improved oxygenation nor lung compliance), have none of these benefits and may be at higher risk of injury form these higher pressures. Currently there is no clear consensus of how to clearly define who might or might not be a responder and how frequently that should be assessed.

2.9. *Prone positioning*

Most patients who are receiving invasive mechanical ventilation in an ICU will be positioned supine with the degree of recumbency being varied, although patients may spend time nursed on their sides (so as to reduce skin pressure which can lead to pressure necrosis of skin). In ARDS, the dependent parts of the lung are much more severely affected. One strategy to improve recruitment of alveoli is to position the patient prone, often for many hours, so as to promote effective ventilation of alveoli in the, previously, dependent parts of the lung.

2.10. *Extracorporeal respiratory support*

Extra-Corporeal Life Support (ECLS) refers to the use of machines to circulate patient blood to support cardiac or ventilatory functions. These circuits require cannula to access and return the blood; a pump to circulate the blood and an oxygenator to add oxygen and remove carbon dioxide. There are two

principal forms of ECLS used to support respiratory function- these are Veno-Venous Extra Corporeal Membrane Oxygenation (VV-ECMO; adds oxygen and removes carbon dioxide) and Veno-Venous-Extra Corporeal Carbon Dioxide Removal (VV-ECCO$_2$R; only removes carbon dioxide).

ECMO can either partially or completely replace the gas exchange requirements of the patient's lungs and the mechanical ventilator. It is invasive and high blood flow rates (4-5L/min) are required to achieve oxygenation and carbon dioxide removal. Larger cannulae are required to achieve the blood flow rates required.

ECCO$_2$R can be used to reduce the intensity of mechanical ventilation. As mechanical ventilation is only required to achieve oxygenation and no carbon dioxide removal much smaller tidal and minute volumes can be used. Furthermore, the blood flow rates required to remove carbon dioxide are much less than to achieve oxygenation (0.5-1.0L/min) and smaller cannulae are required.

2.11. *Spontaneous ventilation and weaning of ventilation*

As lung damage in CAP or CAP with ARDS resolves, it becomes possible for the patient to breathe for themselves. The process by which the patient is transitioned from full mandatory ventilation to fully breathing for themselves, independent of mechanical ventilation, is termed ventilatory weaning. A number of different strategies are used, including trials of spontaneous breathing (either with or without the ventilator providing support for triggered breaths) or gradual reduction of the number of mandatory breaths per minute that are provided by the ventilator during which time the number of Pressure Support breaths that the patient triggers increases commensurately, followed by progressive reduction in the amount of pressure that is provided to support each Pressure Support breath. Ultimately the patient will be extubated and spontaneously breathing or, if a tracheostomy is inserted, will be breathing spontaneously through that device. However, there have been some concerns that the use of pressure support, rather than tightly controlling the tidal volume can potentially lead to lung injury due to large tidal volumes delivered.

2.12. *Interaction between ventilatory strategy and use of sedative agents and paralysis*

Invasive mechanical ventilation requires the placement of a tube into the patient's trachea, typically with an endotracheal tube that enters through the oral cavity and traverses the pharynx and larynx to reach the trachea. Endotracheal tubes are quite uncomfortable, and it is standard practice to administer sedative agents to provide sufficient comfort of the patient and to achieve safety as there

would otherwise be a risk that the patient would remove the endotracheal tube, while dependent on invasive mechanical ventilation. Over time, the amount of sedative medication that is necessary to achieve comfort and safety often decreases. Fully mandatory ventilation often requires higher levels of sedation than mixed mandatory and triggered ventilation or fully triggered ventilation. In some patients, but always in the presence of high levels of sedation, agents that cause muscle paralysis are administered to facilitate fully mandatory ventilation.

As such, different strategies of ventilation may require different levels of sedation or the use of agents that cause paralysis. These differences provide an alternative pathway by which different ventilatory strategies can affect outcome i.e. benefit or harm, with different ventilatory strategies, may arise because of benefit or harm from the sedative or paralysis strategy.

2.13. *Hypoxemic Rescue therapies*

Refractory hypoxemia during mechanical ventilation is generally based on defined and/or unanimously agreed thresholds that would mandate the use of rescue therapies (Hodgson et al., 2013). Although the outcome might vary with different rescue procedures, most of them will improve oxygenation. Commonly used rescue therapies for refractory hypoxemia include prone positioning, recruitment maneuvers, extracorporeal membrane oxygenation etc.

APPENDIX 2: EVIDENCE FOR STRATEGIES FOR DIFFERENT COMPONENTS OF VENTILATORY SUPPORT

1. INTRODUCTION

Despite the incidence of the use of invasive mechanical ventilation for respiratory failure, which is in the order of several million patients per year globally, the total sample recruited into clinical trials of mechanical ventilation strategies over many decades is not more than twenty to thirty thousand patients. As outlined above, one of the complexities for trials of alternative strategies for invasive mechanical ventilation is the array of different components of mechanical ventilation that can be varied in an individual patient including, but not limited to the balance between mandatory and triggered breaths. For mandatory breaths whether Pressure or Volume Control is used, the size of breaths in inspiration, the amount of PEEP, what levels of blood carbon dioxide or oxygen are targeted or regarded as acceptable, the use of prone positioning, the use of extracorporeal support, the use of recruitment maneuvers, and the independent effect of sedation strategy and use of paralytic agents. Furthermore, many of the potential impacts of these components are interdependent, i.e. there is interaction between components. It is also possible that there the treatment effect of some of these components is different, including divergent, for different categories of patients, for example unilateral versus bilateral pneumonia and for different levels of severity of ARDS.

The following sections outline the evidence, derived from randomized trials or inferred from observational studies, regarding the impact of different components of invasive mechanical ventilation on patient outcomes. Most trials of alternative ventilation strategies that have included patients with CAP have enrolled patients with ARDS and there is limited evidence derived from patients with CAP but without ARDS.

1.1. *Characteristics of mandatory inspiratory breaths*

A pivotal RCT compared a strategy of administering Volume Control ventilation to both groups but targeting a low tidal volume of 6 ml/kg PBW compared with a high tidal volume of 12 ml/kg PBW. In the low tidal volume group, a maximum end-inspiratory pressure Pplat of less than or equal to 30 cm H_20 was also targeted. Mortality at hospital discharge, censored after 60 days, was reduced for patients receiving the low tidal volume strategy (31% compared with 40%, P = 0.007) (Acute Respiratory Distress Syndrome et al., 2000). The results of this trial are supported by several other

trials that compared similar differences in tidal volume (Amato et al., 1998, Stewart et al., 1998, Petrucci and Iacovelli, 2004).

Tidal volume is a continuous variable and these trials compared only two tidal volumes and no empiric implications can be drawn about other tidal volumes (Webb et al., 2012). The possibility that tidal volumes below, or above, 6 ml/kg PBW may be equally beneficial or even superior cannot be excluded on the basis of the available evidence from RCTs.

1.1.1. Are tidal volumes below 6 ml /Kg beneficial?

Amato et al demonstrated that the use of lower tidal volume (6 ml/kg PBW) and plateau airway pressures to minimize alveolar strain reduced mortality compared to higher tidal volume (12 ml/kg) (Amato et al., 1998), a finding confirmed in the multi-center ARDSnet study (2000). Laboratory work (Hager et al., 2005) and recent clinical evidence, demonstrate an association 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 cm H_2O appear to be safer (Terragni et al., 2007, Hager et al., 2005). Reducing tidal volume, plateau pressure and driving pressure therefore aims to further minimize alveolar strain.

1.1.1.1. Might tidal volumes above 6 ml /Kg be equally protective compared to 6 ml / Kg

There has been persistent criticisms of the selection of 6 and 12 mls/kg that were used in the ARDSnet trial (Acute Respiratory Distress Syndrome et al., 2000). Post hoc analysis of the ARDSnet study suggested that different groups may exist with divergent effects of tidal volume reduction. Deans et al suggested that while patients with reduced pulmonary compliance have improved outcomes with reduced tidal volume, the patients with higher pulmonary compliance appeared to have higher mortality with low tidal volume ventilation (Deans et al., 2010).

Some have advocated that tidal volumes above 6 mls /Kg, but still less than 12 ml/kg may be equally protective. Interestingly, in mechanically ventilated patients who did not meet the criteria for ARDS, trials have tested strategies targeting 6mls/Kg versus 10mls /Kg and did not report differences in duration of ventilation, although such trials may have been underpowered to detect clinically significant differences (Writing Group for the et al., 2018).

Additional, related, concerns have been raised regarding the interpretation of low versus high tidal volume trials. The trials randomized patients to two distinct strategies without including a 'wild-type' comparison group which would have allowed the treating clinician to specify the tidal volume,

including allowing different tidal volumes for different patients and allowing a personalized approach to setting of target volume. Furthermore, as discussed above the post hoc analysis of the ARDSnet trial suggests possible differential treatment effect with improved outcome from low tidal volume for patients with more severe impairment of lung compliance, but increased mortality from low tidal volume for patients with less severe impairment of lung compliance (Deans et al., 2010). This finding is particularly relevant in extrapolating the results of trials that enroll patients with ARDS to patients with CAP with unilateral pneumonia or bilateral pneumonia but without having severe ARDS.

Another uncertainty, regarding optimal tidal volume is, irrespective of what is the ideal tidal volume, whether achieving this tidal volume with Pressure Control ventilation would achieve the same outcome. This question, in turn, leads to a further question, as to whether outcomes would be better if, rather than targeting a pressure rather than a volume. Options would be change in pressure (delta P or Pplat. Interestingly, recent re-analysis of the 6ml/Kg arm of the tidal volume trials has suggested that a lower driving pressure (Plateau Pressure – PEEP) rather than absolute PEEP or Driving Pressure was strongly linked with survival (Amato et al., 2015). This work suggested that a ventilation strategy which aimed to limit driving pressure could potentially be beneficial. Some clinicians now adjust ventilatory settings to try and reduce elevated driving pressures despite any prospective trial suggesting this approach is beneficial.

1.1.2. Positive End Expiratory Pressure (PEEP)

The majority of ICU clinicians will agree that the correct selection of PEEP for a patient with CAP, either with or without ARDS is important. However, there will be little agreement on what is the correct level and how best to select it. How best to select PEEP has been one of the most vexed questions in critical care(Rouby et al., 2002, Brochard, 2010). Various techniques have been proposed, including a) pulmonary mechanics (i.e. using super-syringe, plateau pressure etc.) (Amato et al., 1998, Villar et al., 2006, Mercat et al., 2008), b) CT guided (Brochard, 2010) and c) FiO_2/PEEP algorithms (2000, Brower et al., 2004). However, these techniques have been criticized 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) (Minneci et al., 2008, Tuxen and Hodgson, 2010).

1.1.2.1. PEEP: FiO_2 tables

One approach was to couple an increasing level of PEEP with a given F_iO_2. This approach gained some traction in trials. It was simple to protocolize and made some physiological sense as generally increased PEEP would help improve oxygen transfer in hypoxic patients with high F_iO_2 requirements.

1.1.2.2. PEEP in tidal volume trials

The PEEP: FiO_2 table was first used in the ARMA ARDSnet trial to titrate F_iO_2 and PEEP. The PEEP level in the table below 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.

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 (cm H_2O)	5	5	8	8	10	10	10	12	14	14	14	16	18	18-24

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 skip from left to the right of the chart achieve a satisfactory saturation, then refine to achieve a of SaO_2 90 – 95%.

While popular in trials there has been limited adoption into clinical practice.

1.1.2.3. Different PEEP strategy trials

The optimal strategy for determining PEEP is not known. Several methods of setting PEEP have been developed including a) titration to pulmonary mechanics (i.e. using super-syringe, plateau pressure etc.) (Amato et al., 1998, Villar et al., 2006, Mercat et al., 2008), titration based on CT scanning (Brochard, 2010) and FiO_2/PEEP tables (2000, Brower et al., 2004). However, all techniques, other than PEEP:FiO_2 tables are one or more of 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) (Minneci et al., 2008, Tuxen and Hodgson, 2010, Brower et al., 2004, Meade et al., 2008, Mercat et al., 2008).

Three large randomized trials compared high and moderate PEEP strategies using low tidal volumes in both groups (Brower et al., 2004, Meade et al., 2008, Mercat et al., 2008).None of these trials

demonstrated a reduction in mortality with higher levels of PEEP. However, a subsequent meta-analysis suggested a small survival benefit from the high PEEP strategy in the subgroup of patients with more severe ARDS (PaO_2:FiO_2 < 200) (Briel et al., 2010). Furthermore, two of these trials which defined refractory hypoxemia *a priori*, demonstrated that high PEEP strategies led to significantly fewer episodes of refractory hypoxemia and required fewer rescue therapies. These finding highlight the intricate interactions between PEEP, Tidal volume and driving pressure. In addition, higher levels of PEEP may be beneficial in severe ARDS but not mild / moderate ARDS patients (Briel et al., 2010), suggesting the previous inclusion of mild / moderate ARDS patients in prior studies may have diluted their potential to detect a protective effect (Amato et al., 1998, Brower et al., 2004, Meade et al., 2008).

Despite, these concerns higher PEEP strategies have been advocated for patients with severe acute respiratory distress syndrome (REF), as it decreases refractory hypoxemia. The recent LUNGS SAFE study demonstrated that many clinicians do not use elevate levels of PEEP despite high F_iO_2 (Bellani et al., 2016). This suggests significant clinical uncertainty. Clinicians require high level evidence to guide PEEP titration in patients with moderate and severe ARDS.

1.1.3. Interaction between PEEP and size of inspiration

Previous trials have been criticized for mandating similar tidal volume strategies in both the low PEEP and high PEEP arms, resulting in increased airway pressures in the high PEEP arms, thereby potentially confounding the protective effects of the higher PEEP. Furthermore, the previous trials incorporating higher levels of PEEP did not assess individual patient responses to the elevation or reduction in PEEP. It has been demonstrated that patients who have improvements in oxygenation in response to elevations in PEEP had improved outcome compared to those patients who didn't.

1.1.4. Open Lung Strategies incorporating Recruitment maneuvers and elevated PEEP

An Open Lung Strategy (OLS) is a strategy that aims to recruit as many alveoli as possible to participate in ventilation. They incorporate Lung Recruitment Maneuvers (LRMs) to open recruitable alveoli and elevated PEEP to keep them open during safe tidal volume ventilation.

Only one study of a LRM with "higher" PEEP has demonstrated a survival advantage (Amato et al., 1998), 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 protocolized higher PEEP levels, with low tidal volume, with or without LRMs, failed to demonstrate a survival advantage but decreased severe hypoxemia (Meade et al., 2008), decreased the need for hypoxemic rescue therapies (Meade et al., 2008) and increased ventilator free days (VFDs) (Mercat et al., 2008). However, the ability of these

studies to have realized 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. In particular the use of LRMs which used inadequate pressures for inadequate periods of time, used low levels of PEEP after the LRM or didn't aim to further limit driving pressures. Three trials have subsequently attempted to address these concerns. The OLA trial (Kacmarek et al., 2016) which halted recruitment prematurely due to slow trial patient enrolment, showed a non-significant trend towards reduced mortality. The ART trial (Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial et al., 2017) demonstrated an increase in mortality with an OLS compared to 6mls /Kg (ARDSnet). However, this trial was criticized for a very high mortality in both the interventional and control groups and for a method for selecting PEEP which may have predisposed to air trapping and lung over dissension. Finally, the PHARLAP trial (Hodgson et al., 2019) which stopped early (N=115) after publication of the ART study did not demonstrate any of the signals to harm which were demonstrated in the ART study. The question of whether an OLS may be beneficial in patients with ARDS is still unanswered. A planned IPDMA between these investigators may highlight patient characteristics (i.e. recruitable lung or not) that may allow personalization of the OLS to a population that will benefit.

1.1.5. Prone positioning

Prone positioning has been used in mod / severe ARDS to improve oxygenation. Randomized, controlled trials have confirmed that oxygenation is significantly better when patients are in the prone position than when they are in the supine position (Abroug et al., 2008, Sud et al., 2010). In addition, it had also been suggested that prone positioning may also reduce VILI and improve patient outcomes (Kamo et al., 2018, Sud et al., 2014, Mentzelopoulos et al., 2005, Messerole et al., 2002). However, this did not translate into better outcomes in all trials. In 2013 the PROSEVA Trial (Guerin et al., 2013) tested whether early prone positioning for at least 16 consecutive hours per day until improvement in ARDS patients, up to day 28, versus standard supine ventilation reduced all cause morality at day 28. In 474 patients randomized over 3 years the trial demonstrates a 16% morality for prone compared with 32.8% for supine (P<0.01; OR 0.42 (0.26-0.60)) with no increase in adverse events. Interestingly, the adoption of prone positioning into for ARDS routine clinical practice has been sporadic which practice adoption largely being along national boundaries.

1.1.6. Neuro Muscular Blocking Drugs (Paralysis)

Clinicians have used neuromuscular blocking (NMB) agent in patients with ARDS and severe CAP for decades. The use of NMBs has been proposed to help these patients by promoting ventilation synchrony, reducing work of breathing and reducing alveolar fluid accumulation but this may come at

the expense of acquired muscular weakness. The ACURASYS trial (n=340, JAMA 2010) demonstrated a statistically significant reduction in morality in patients with moderate or severe ARDS treated with cisatracurium with deep sedation vs deep sedation alone (Papazian et al., 2010). However, the subsequent early neuromuscular blockade in ARDS trial (n=1006, ROSE Trial) did not demonstrate any significant difference in morality 90 days between patient who received an early cisatracurium infusion versus those treated with standard care (National Heart et al., 2019). Currently, NMBs are not use routinely in early ARDS but reserved for significant patient: ventilator dysynchrony.

1.1.7.APRV

APRV is a mode of ventilation that has been in use for more than 30 years, both as a therapy to prevent severe respiratory failure in patients receiving mechanical ventilation and as a rescue therapy for patients with established severe hypoxic respiratory failure unresponsive to conventional modes of mechanical ventilation (Garner et al., 1988, Andrews et al., 2013, Lim et al., 2016). International data suggests that the use of APRV is widespread, across a range of causes of respiratory failure, but that there are substantial geographical differences in use (Gonzalez et al., 2010).

Observational studies suggest that the safety of APRV ventilation in patients with severe hypoxemic respiratory failure, including mortality, cardiovascular deterioration and incident barotrauma, is comparable to alternative ventilatory strategies. Observational data also suggests that APRV ventilation is effective in improving oxygenation and may reduce the requirement for alternative rescue modalities and sedation requirements (Marik et al., 2009). In a single center study, Lim et al reported that APRV ventilation was associated with a low requirement to initiate ECMO in a cohort of patients with severe ARDS (Andrews et al., 2013).

A multicenter feasibility RCT by Hirshberg et al compared low tidal volume (<=6ml/kg) using volume control to APRV in patients with acute hypoxic respiratory failure (Hirshberg et al., 2018). Participants were randomized to one of three arms, traditional volume control, 'traditional' APRV, or APRV with a goal of limiting release Tv to <6.5ml/kg by adding extrinsic PEEP to Plow. The study was stopped early, after 52 of the planned 246 patients were enrolled, due low recruitment and an inability to limit release phase Tv in the low Tv APRV group. No significant differences in clinical outcomes were observed between the groups. Whether large release phase Tv may be harmful remains uncertain. However, in a recent systematic review and meta-analysis of seven RCTs (n=412) (Lim and Litton, 2019), including adult patients receiving APRV ventilation for acute hypoxemic respiratory failure, APRV was associated with a significant mortality benefit (relative risk [RR] 0.67; 95% confidence interval [CI] 0.48-0.94; I^2<0.1%; p=0.97) and improvement in day-three PaO_2/FiO_2 ratio (weighted

mean difference 60.4; 95% CI, 10.3-110.5). There was no significant difference in requirement to initiate rescue treatments including inhaled pulmonary vasodilators, prone positioning or extracorporeal membrane oxygenation (RR 0.51; 95% CI, 0.22-1.21; I^2=64.7%; p=0.04). The risk of barotrauma was only reported in three studies and did not differ between groups (RR 0.39; 95% CI, 0.12-1.19; I^2<0.1%; p=0.99). Given the limited number of patients enrolled in the available studies, larger RCTs are required to validate these findings.

1.1.8. ECMO

VV-ECMO is a form of ECLS which adds oxygen and removes carbon dioxide and may improve lung rest and reduce VILI. It has been previously used as a rescue therapy used in extreme life-threatening hypoxemia or hypercapnia. However, increasingly it is being considered in less extreme ARDS as an intervention which may facilitate protective ventilation. VV-ECMO requires is a highly invasive treatment and is associated with significant complications. The CESAR Trial (Peek et al., 2006) showed that referral to an ECMO center for the consideration of ECMO improved outcome in patients with severe ARDS. However, many patients referred did not actually receive ECMO and treatment in the control group (no referral to specialist center) was not standardized. It was suggestive but still unclear if ECMO was beneficial in severe ARDS. In his context, the ECMO for severe ARDS trial (EOLIA trial) randomized 249 patients with severe ARDS to either receive early VV-ECMO or protective mechanical ventilation (ARDSnet). This study found no statistical difference in morality at 60 days, ECMO group 35% versus control ventilation of 46% (p=0.04, RR 0.76 (0.55-1.04). However, 28% of the control group patients crossed over to receive ECMO, significantly confounding he ability to detect a significant benefit of ECMO in this cohort (Combes et al., 2018).

1.1.9. $ECCO_2R$

An $ECCO_2R$ strategy is a combination of ECLS to remove carbon dioxide (not adding oxygenation) and a mechanical ventilator providing sufficient ventilation to achieve adequate oxygenation. This approach allows the ventilator to used tidal volumes below 6mls/Kg and to achieve low plateau pressures. There is some data to suggest that lower tidal volume and lower driving and plateau pressure may be beneficial. However, to date there is little clinical trial data to suggest $ECCO_2R$ is beneficial. Despite this, $ECCO_2R$ is being adopted into clinical practice. In this context the pragmatic pRotective vEntilation With Veno-venouS Lung assisT in Respiratory Failure (REST trial; https://clinicaltrials.gov/ct2/show/NCT02654327) will aim to answer whether ECCO2R in superior to current standard practice.

1.1.10. Hypoxemic Rescue therapies

When ARDS is severe, high-inspired oxygen concentrations are frequently required to minimize hypoxemia. In these situations, clinicians commonly utilize interventions termed 'hypoxemic rescue therapies' in an attempt to improve oxygenation (Hodgson et al., 2013), as without these, conventional mechanical ventilation can be associated with high mortality. However, their lack of efficacy on mortality when used prophylactically in generalized ARDS cohorts has resulted in their use being confined to clinical trials and the subset of ARDS patients with refractory hypoxemia. First line hypoxemic rescue therapies include inhaled nitric oxide, prone positioning, alveolar recruitment maneuvers and high frequency oscillatory ventilation, which have all been shown to be effective in improving oxygenation. In situations where these first line rescue therapies are inadequate extra-corporeal membrane oxygenation has emerged as a lifesaving second line rescue therapy. Rescue therapies in critically ill patients with traumatic injuries present specific challenges and requires careful assessment of both the short- and longer-term benefits, therapeutic limitations, and specific adverse effects before their use. Therefore no commonly-agreed strategy for the timing and order of use of hypoxemic rescue therapies currently exists, and clinicians must balance these factors before making a decision.

1.1.11. Spontaneous ventilation and weaning from ventilation

Increasingly commonly, patients are being transitioned from controlled mechanical ventilation strategies to spontaneous modes of ventilation. Spontaneous breathing during mechanical ventilation is more physiological but is associated with both advantages and disadvantages. Transition to spontaneous breathing is necessary for weaning from the ventilator. Weaning can be considered once the underlying process necessitating mechanical ventilation is resolving. Weaning is the process of liberation from, or discontinuation of, mechanical ventilatory support. Weaning comprises 40% of the duration of mechanical ventilation

1.1.12. Challenges associated with ventilation trials

Despite millions of patients with severe CAP with or without ARDS requiring mechanical ventilation each year, the amount of high-quality trial information being produced is very limited. As the previous sections demonstrate, the choice of mechanical ventilation strategies and individual mechanical ventilation settings available for the treating clinician are vast. In addition, severe CAP / ARDS is a dynamic process with changes occurring in the diseased lungs which further impacts the titration of these settings. These complex interactions have proven difficult to protocolize adequately for some clinician's satisfaction. This has caused some clinicians to be reluctant to randomize into a given

ventilation protocol and to vary ventilation based on their previous clinical experience. This can result in non-representative samples being included in trials which impacts he generalizability of the results and he cycle continues. Furthermore, a significant proportion of patient with severe CAP / ARDS develop significant hypoxemia. Here are a number of rescue therapies available for severe hypoxemia, however, the evidence supporting each is weak and clinician's preferences are based on experience and availability of individual therapies. This further complicates ventilation trials with clinicians potentially crossing over patients who meet severe hypoxemia thresholds into treatments which commonly have features of the intervention group. This was clearly a problem for the EOLIA Trial which has a control of ECMO crossover rate of 28% (Combes et al., 2018).

Mechanical ventilation is a complex intervention delivered in the critically ill patient. Furthermore, in various regions mechanical ventilation settings are determined by difference craft groups (doctors, nurses, respiratory therapists etc.). Finally, the ability to ensure consistent adherence to a complex protocol, across multiple craft groups, in critically ill patients during a dynamic process is challenging to say the least.

These are some of the reasons for the limited number of mechanical ventilation trials to date.